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REVIEW

The Clam Cystoplasty

F. J. BRAMBLE

Department of Urology, Bournemouth General Hospital, Bournemouth

The young adult or teenager with an unstable bladder is a therapeutic challenge. Symptoms of urge incontinence and nocturnal enuresis are degrading, demoralising and disrupt both domestic and social life. A visit to the urologist, delayed by embarrassment, is often provoked by impending marriage, which brings the whole problem into focus.

The first-line treatment is an adequate dose of an anticholinergic agent supported by some kind of bladder drill. For those who fail to respond to anticholinergics some authors recommend bladder transection. Hindmarsh *et al.* (1977) reported a cure or improvement in 53% of patients by transection, but the results were poor if the passive bladder capacity was less than 400 ml. Mundy (1983) reported 65% relieved of symptoms at 2 to 5 years but noted that those patients who failed to respond to anticholinergics also failed to respond to transection (Mundy, 1986). He now offers transection only to those patients who respond to anticholinergics but cannot tolerate their side effects. In my hands, transection has unreliable results and when improvement does occur it seldom lasts for more than a few months. Lucas and Thomas (1987) had equally disappointing results with endoscopic transection.

Transvesical injection of the pelvic plexuses with phenol is another option to be considered. Blackford *et al.* (1984) obtained good results in 69% of women over the age of 55 years, but in younger women, who more commonly present with instability, only 14% had a satisfactory response. Phenol injection is contraindicated in men because it causes impotence. Other complications are few but include the occasional sciatic nerve palsy. Perhaps phenol injection is best reserved for the non-ambulant neuropathic patient with detrusor hyper-reflexia.

Patients with the most severe symptoms of idiopathic instability often fail to respond to conservative treatment; for these patients the "clam" cystoplasty is a realistic alternative.

Technique

Theoretical considerations and previous experience suggested that a simple patch or cup augmentation enterocystoplasty would result in a diverticulum, since the unstable detrusor muscle tends to evacuate the high pressure vesical element into a separate low pressure compartment (Turner-Warwick and Ashken, 1967). The "clam", which almost completely bisects the bladder, was developed in an attempt to overcome this problem.

The original technique (Bramble, 1982) has stood the test of time. The operation has since been described in some detail elsewhere (Mundy, 1985, 1986) but the crucial elements of the procedure deserve emphasis. The bladder is bivalved almost completely in the coronal plane (Fig.). The incision is carried to within 1.5 cm of the internal urethral meatus, just anterior to the ureteric orifice on each side. The prepared bladder thus has the appearance of an open scallop or clam, from which the operation takes its name. Others have since bivalved the bladder in the sagittal plane with similar results. The bivalving incisions must be carried close to the internal urethral meatus to ensure deactivation of the unstable detrusor muscle.

A length of pre-terminal ileum, equal in length to the bladder defect, is isolated on its own blood supply and detubularised by incising the antimesenteric border. The ileal patch is sutured into the bladder defect with a single layer of continuous vicryl. Ileum is used in preference to colon because it has a lesser risk of malignant change. A patch of sigmoid colon can be used if the ileum has a very short mesentery or is unavailable.

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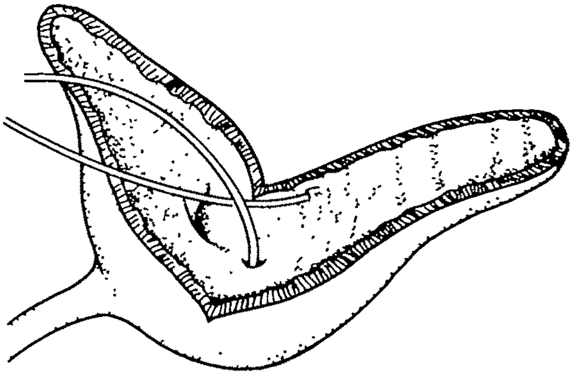

Fig. Bladder preparation for the clam cystoplasty

Results in Idiopathic Instability

The operation is considered to have a satisfactory result if diurnal and nocturnal incontinence ceases and frequency and urgency are significantly reduced. Thirteen (86%) of an original group of 15 patients were voiding spontaneously and satisfied these criteria at a mean follow-up of 30 months (Bramble, 1982). The 2 remaining patients were also continent but required clean intermittent self-catheterisation (CISC) because of voiding difficulty. Patients measured their own maximum comfortable bladder capacity; the mean value increased from 230 to 554 ml.

Mundy and Stephenson (1985) reported results in 40 cases; 36 (90%) were cured at a mean follow-up of 12 months; 30 of these were voiding spontaneously and 6 by CISC. In post-operative video-urodynamic (VUD) studies they found that the mean bladder capacity increased from 280 to 615 ml, but there was a mean residual volume of 175 ml. The mean *functional* bladder capacity was thus increased from 280 to 440 ml. Low bladder compliance became normal in 14/20 patients (70%). Compliance was improved in 4 others and was worse in 1 patient. In 26 patients with pre-operative instability or hyper-reflexia, the instability was abolished in 15 (57%). The remaining 11 had persistent instability but this was asymptomatic and generated significantly lower pressures than before operation. These results have since been confirmed in other centres. Recurrence of high pressure contractions and relapse of symptoms have not proved to be a problem (McRae *et al.*, 1987; Lewis *et al.*, 1990).

Some young adults with primary nocturnal incontinence have normal urodynamics but still benefit from the clam (Bramble, 1982). Lewis *et al.* (1990) treated 20 such patients with the clam, the age range being 8 to 31 years (average 17); 18 patients became continent (90%), 10 voiding spontaneously and 8 requiring CISC. McInerney *et al.* (unpublished data) studied 24 such patients with overnight cystometry and in 10 cases found prolonged high pressure unstable contractions which were not revealed by conventional cystometry.

How does it Work?

Post-operative VUD studies suggest that a number of factors contribute to the symptomatic improvement. Bivalving the bladder splits the circular continuity of the detrusor fibres and converts a spherical organ into 2 flat plates. This either abolishes unstable activity or makes any residual contractions less effective (Mundy and Stephenson, 1985). Secondly, the interposition of an intestinal segment, which has been detubularised to abolish its own contractile activity, tends to absorb any residual detrusor activity. Finally, the total and functional volume of the bladder is increased. It seems probable that a combination of these factors contributes to the success of the clam.

Problems and Complications

Post-operative complications are those which might be expected from any major operation involving bowel and bladder. If care is taken with the anastomosis between ileum and bladder, post-operative urinary fistula is rare. Bleeding can occur at the angle of the clam if the branches of the inferior vesical vessels are not adequately included in the haemostatic suture.

The object of the clam is to make detrusor contractions ineffective, so it is not surprising that the main post-operative problem is voiding difficulty with relative bladder outflow obstruction. Nearly all patients have to strain to empty the bladder. Because this voiding imbalance is so common, every patient must be followed up closely during the first few months, and success of the operation often depends on the management of this problem.

Residual volume is best monitored by ultrasound as repeated catheterisation can reintroduce infection. If the patient is voiding reasonable volumes without undue discomfort or frequency, a moderate residue can be accepted and the patient allowed home. Most patients take 2 or 3 months to adapt to their new bladder and to learn to void effectively by abdominal straining. Occasional nocturnal incontinence during this period is not unusual. If the residual volume is high and accompanied by significant frequency, voiding difficulty or persistent urinary infection, a VUD study is performed. About 20% of patients who subsequently void spontaneously will require rebalancing procedures (Bramble, 1982; Mundy and Stephenson, 1985). Rebalancing is accomplished either by bladder neck incision or Otis sphincterotomy, or both, as indicated by serial videos (Turner-Warwick, 1979). Most male patients will require a bladder neck incision; indeed Mundy and Stephenson (1985) do this routinely, either pre-operatively or at the time of operation. Young males, however, may wish to preserve ejaculation and although this cannot be guaranteed it is sometimes possible. I have 2 such patients who have been voiding spontaneously for over 7 years with intact bladder necks.

Some patients cannot void effectively even after rebalancing. Clean intermittent self-catheterisation is needed in as many as 30%. It is not possible to predict which cases will require CISC, so all patients should be warned of this possibility and trained to self-catheterise before operation. CISC may also be a useful temporary measure during the period of stabilisation in the first few weeks after operation (Mundy, 1986). Although the need for CISC might reasonably be regarded as failure of the clam operation, the previously incontinent but now dry patient is usually pleased with the result.

Minor and moderate degrees of stress incontinence due to sphincter weakness should not be treated at the time of the clam (Mundy and Stephenson, 1985). Stress incontinence is rarely a persistent problem and makes the patient less prone to post-operative voiding difficulties. If stress incontinence persists it can be treated by a cautious endoscopic colposuspension.

Some patients have difficulty in voiding mucus. Mucus production seems to diminish somewhat with time but never stops entirely. In a few patients the mucus aggregates into marble-shaped balls which have to be removed endoscopically. Persistent or recurrent urinary infection is a problem in a significant minority of patients, particularly females, and is best managed by a long-term prophylactic antibiotic. Disordered acid-base balance with hyperchloraemic acidosis does occur (Nurse and Mundy, 1989a) but it is mild and rarely requires bicarbonate replacement.

Late major complications are few but include spontaneous perforation of the neobladder at the site of the suture line, leading to a localised urinoma or generalised peritonitis. The pathogenesis of this complication is not understood and does not appear to be associated with traumatic CISC. Only 1 patient under my care, a young male, has perforated spontaneously on 2 separate occasions after a heavy beer drinking session followed by deep sleep.

Patch diverticulisation may occur if the bladder has been inadequately bisected, since the suture line tends to contract and thus leads to an hourglass deformity (Mundy, 1988). Patch shrinkage has occurred in 1 of my patients with reduction of bladder compliance. This was successfully managed by a second clam. In the female, the mesentery to the ileal patch lies across the body of the uterus, but there have been a number of successful pregnancies with no reported complications.

After a lifetime of nocturnal incontinence some younger patients are so pleased with the results of their operation that they find it difficult to accept the need for careful follow-up. The altered dynamics of the bladder must be explained to the patient so that the need for continued supervision is appreciated.

There have been few reports of tumours occurring at the ileo-vesical junction in augmentation cystoplasties (Stone *et al.*, 1987), and no tumour has yet been reported in a clam. The use of a colonic patch carries a much higher risk. Nurse and Mundy (1989b) found high levels of urinary N-nitrosamines which correlated with heavy bacterial growth on urine culture in both colonic and ileal cystoplasties. The concentration of these carcinogens was higher when a colonic patch was used but high levels were also found in ileocystoplasties with associated inflammation of the bowel mucosa and squamous metaplasia affecting the urothelium. Ileum has been used to augment the bladder for a very long time and the risk of tumour is known to be small. Reported cases almost always have very large volumes of residual urine with chronic infection. The latent period to presentation is often more than 20 years, but at least 1 case has presented at 7 years. Thus careful follow-up of the clam should include cystoscopy at annual intervals and the effective control of urinary infection.

The Failed Clam

Success or failure of the operation is usually clear within the first few months and late failure is rare (Lewis *et al.*, 1990). Persistent incontinence may require substitution cystoplasty with CISC or even a continent diversion. The choice of further treatment will be dictated by individual circumstance, but if there has been some measure of improvement the patient may opt for the imperfect results of the clam.

The Clam for the Neuropathic Bladder

Because the clam proved to be the most effective treatment for idiopathic instability resistant to conservative treatment, it was not long before the operation was tried in patients with neuropathic bladders who would previously have been treated by substitution cystoplasty (Stephenson and Mundy, 1985).

McRae *et al.* (1987) treated 59 patients. The majority were ambulatory cases of myelodysplasia but the group included cases of spinal tumour, multiple sclerosis, spinal injury and transverse myelitis. The indication for operation in most of these cases was incontinence due to hyper-reflexia or severely reduced compliance. Impaired renal function was a factor in 17 cases. In 7 cases the clam was performed as part of undiversion and 22 patients also required insertion of an artificial urinary sphincter (AUS). There was a significant complication rate in this complex group but satisfactory results were obtained in 42 patients (72%) who were continent with stable upper tracts; 13 of these patients were managed by CISC.

Because the clam technique is quicker and easier to perform than a substitution cystoplasty it considerably reduces the magnitude of the surgery. McRae *et al.* (1987) concluded that the clam cystoplasty is the procedure of choice when the bladder is not too severely diseased and fibrotic. Parry *et al.* (1990) further defined the role of the clam in the treatment of the neuropathic bladder and in particular its use in conjunction with the AUS.

American urologists have concentrated more attention on the source and configuration of the bowel segment in augmentation cystoplasty and less attention has been paid to the shape of the residual detrusor component (Goldwasser and Webster, 1986). Sidi *et al.* (1990) used a colonic cup patch with a clam reconfiguration of the bladder in 12 spinal cord injury patients. At 15 months all patients were continent on CISC with stable upper tracts. Strawbridge *et al.* (1989) used a clam augmentation cystoplasty with the AUS in 18 neuropathic cases of incontinence due to poor bladder compliance with sphincteric incompetence. All 18 patients attained continence, 15 with the help of CISC. All but 2 of these patients had refashioning of the bowel segment into a cup shape. The UK experience would suggest that reconfiguration of the bowel is unnecessary unless the detrusor is very thickened and fibrotic.

Conclusions

Experience with the clam since 1982 has further defined the scope and indications for this operation. The clam cystoplasty is not the answer to the occasional episode of urge incontinence. It is a major operation with significant complications and should be reserved for patients with severe symptoms who have not responded to conservative treatment.

Idiopathic instability

The treatment of idiopathic instability by the clam is well within the capability of the urologist with a general surgical background who has access to adequate urodynamic facilities. Good results can be expected in idiopathic instability, particularly in the younger patient, providing the urologist is prepared to give time to post-operative reassessment and careful rebalancing.

Nothing is gained by delaying treatment beyond the late teens if symptoms are severe.

Those cases of post-prostatectomy incontinence where instability is the underlying cause respond well to the clam providing there is no co-existing brain failure.

The neuropathic bladder

The use of the clam in the reconstruction of the neuropathic bladder may benefit even more patients, but the treatment of this complex group of cases is not within the scope of the general urologist. It often involves the use of an AUS and should be confined to specialised centres.

The clam plays a major role in:

(1) Patients with drug-resistant hyper-reflexia where the detrusor is not too severely fibrotic and diseased.
(2) Bladders with poor compliance, with or without sphincter incompetence, which are unaffected by tuberculosis, interstitial cystitis or radiation.
(3) Undiversion, providing the bladder capacity on cycling reaches at least 150 ml.

The Future

For the present, the clam is the most reliable treatment available for severe instability and hyper-reflexia. Unlike transection and subtrigonal injection of phenol, late relapse of symptoms does not occur. Future research needs to concentrate on the underlying pathophysiological abnormality affecting the detrusor and its innervation. We must hope that this will lead to a pharmacological cure which will render the clam obsolete before some of these patients develop long-term complications. Because no detrusor muscle is excised, a pharmacological cure might permit reversal of the clam with excision of the potentially hazardous bowel segment.

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The Author

F. J. Bramble, MS, FRCS, Consultant Urologist, The Royal Victoria Hospital, Shelley Road, Bournemouth BH1 4JG.

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Sedoanalgesia in Urology: A Safe, Cost-effective Alternative to General Anaesthesia

A Review of 1020 Cases

B. R. P. BIRCH, K. M. ANSON and R. A. MILLER

Departments of Minimally Invasive Surgery, Royal Northern Hospital and Institute of Urology, London

Summary—Sedoanalgesia is a technique developed to provide safe and satisfactory operating conditions for a wide range of patients independent of age and overall level of fitness (although its use in children remains to be established). It is suitable for both endoscopic and open procedures, day-cases and in-patients. When used in day-case surgery it significantly improves overall efficiency.

It is recognised that day-case surgery is an important and cost-effective element in surgical care. With increasing restraints being imposed upon hospital finances, patient beds and staffing levels, any strategies designed to improve efficiency in this sphere of surgical activity are to be welcomed. That 93% of patients prefer sedoanalgesia to conventional general anaesthesia attests to its high degree of acceptability. The technique of sedoanalgesia, its applications and potential impact for urology are detailed.

For elderly or unfit patients who require surgery, a local anaesthetic technique is often the procedure of choice. Given that such a technique is suitable for a high-risk group of patients, it should also be appropriate for healthier patients. This situation parallels that for percutaneous nephrolithotomy – initially used in patients unfit for conventional open surgery and subsequently employed more universally when its benefits were established (Birch and Miller, 1989).

There can be little doubt that a technique during which the patient remains co-operative and with physiological reflexes intact has inherent advantages over one where the subject is rendered unconscious and in need of airway protection, as is the case with general anaesthesia. In addition, the high incidence of side effects reported after general anaesthesia for day-case surgery (Fahy *et al.*, 1969; Smith and Young, 1976; Routh, 1979) has led several authors to state that wider use should be made of local anaesthetic techniques (Ogg *et al.*, 1979; Routh, 1979). Not only are such techniques safer than general anaesthesia, but patients express a marked preference for them (Rodrigo and Clarke, 1986; Rassam and Thomas, 1989; Birch *et al.*, 1990a).

In urology many procedures, both endoscopic and open, may be performed under local anaesthesia alone. However, patients are often frightened or embarrassed at the prospect of procedures performed in this way. It has been stated that flexible diagnostic cystoscopy is well tolerated under local anaesthesia alone (Fowler, 1984). Nevertheless, patients are still anxious and, even in a selected population, 20% will require a second admission for definitive surgery. Conventional rigid cystoscopy offers greater scope for therapeutic intervention but is not well tolerated in men using topical local anaesthesia alone. Acceptance by patients of such procedures can be considerably improved by the administration of an anxiolytic agent (Hanno and Wein, 1983) and the use of new low trauma instrumentation (Miller *et al.*, 1987).

The increasing use of minimally invasive tech-

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989 niques in urology has led to a reduction in anaesthetic requirements. Sedoanalgesic techniques have been developed as a direct response to this. The term sedoanalgesia has been chosen to give equal emphasis to the 2 components of this technique—sedation and analgesia. It is recognised that the use of sedatives to complement local anaesthesia in this way is not new (Goerig *et al.*, 1989). However, the techniques described in this report exploit recent advances in instrument technology, local anaesthetic delivery systems and drug research which serve to give sedoanalgesia a distinct nature.

We report our initial experience with 1020 patients and discuss the technique and its applications in urology.

Patients and Methods

Premedication

A premedication is administered 20 to 30 min before surgery. For this purpose midazolam is given by intramuscular injection into the deltoid, vastus lateralis or gluteal muscles. The dose depends on the weight, age and fitness of the patient. In general, we use 5 to 7.5 mg for patients under 70 kg and 7.5 to 10 mg for heavier patients. This is equivalent to 0.1 to 0.12 mg/kg. For young, fit, anxious patients the upper limit of this range is appropriate but in unfit and elderly patients, increased sensitivity to the effects of benzodiazepines demands an appropriate reduction in dosage (30–60%). If in doubt it is better to give too little rather than too much midazolam. It should be noted that the use of such premedication in children remains to be established. Paracetamol (2 tablets) is given at the time of premedication to provide post-operative analgesia in minor cases. Antibiotics are given as appropriate.

Between 10 and 15 min after premedication the urethra is anaesthetised (for endoscopic procedures) using 2% lignocaine applied topically as a gel. In men a penile clamp is used to retain the gel within the urethra. In women, as an alternative to the use of conventional dispensers, the urethra may be anaesthetised by means of 2% lignocaine gel applied to a small cotton swab on a stick which is then positioned in the urethra. Additional analgesia can be achieved by applying lignocaine as a 4% spray to the perineum immediately adjacent to the external urethral orifice. Thus the patient is rendered calm and mildly sedated prior to transfer to the operating theatre. The amnesic effect of midazolam also ensures that most patients do not recall either the application of the topical anaesthetic (or the local anaesthetic block in open procedures) or the operation itself.

Operative Procedures

General

In order to reduce levels of sensory stimulation the ambient lighting level in theatre is lowered and noise kept to a minimum. Background music is also helpful in this respect.

As a routine measure, all elderly and ASA (American Society of Anesthesiologists) grade III or IV patients receive supplemental oxygen by means of nasal cannulae and are monitored using a pulse oximeter. Continuous ECG and automatic blood pressure monitoring (Dinamap) are also available.

The patient must be monitored peri-operatively by surgical staff or anaesthetic colleagues. The latter are obviously more appropriate for sick patients (ASA grades III and IV) or those undergoing major surgery. A nurse should be delegated to speak to and reassure the patient throughout the procedure. Intravenous access by means of a forearm cannula is established in patients requiring transurethral resection and a normal saline infusion commenced.

Those patients about to undergo surgery who are still anxious when they arrive in theatre may require supplemental intravenous midazolam before the procedure begins. This should be given slowly, in increments of 1 mg, the dose being titrated against clinical effect. In general, 1 to 3 mg are adequate.

Endoscopic Procedures

Cystoscopy

All cystoscopies are performed using a small calibre, low trauma Integrated Cystoscope (GU Manufacturing) (Miller *et al.*, 1987). With the patient in the extended lithotomy position the endoscope is introduced into the bladder in the standard fashion. It is helpful before traversing the region of the external sphincter in males to apply pressure to the irrigating system so as to encourage sphincter relaxation. Once in the bladder, standard vesical examination is performed. This is done most easily by starting at the bladder dome and working down to the trigone and bladder neck.

Vesical Procedures

Biopsy

Semi-rigid biopsy forceps (7F) or the purpose-designed Endocut automatic tissue core biopsy needle (Cook Urological) (Fig. 1) can be introduced into the bladder using the instrument channel of the Integrated Cystoscope for the purposes of bladder biopsy. Biopsies of areas outside the trigone may be accomplished without additional local anaesthesia. Otherwise, biopsy is performed following the submucosal injection of 1% lignocaine plain using an Endoneedle (Fig. 2). Trigonal biopsy is best preceded by submucosal lignocaine.

Diathermy

Diathermy of small, superficial bladder tumours, abnormal epithelial areas or bleeding surfaces following biopsy can be achieved using a 7F mono- or bi-polar probe passed via the instrument channel of the Integrated Cystoscope (Fig. 2). The guidelines concerning local anaesthetic use outlined above apply.

Transurethral resection of bladder tumour

The tumour is initially evaluated with the Integrated Cystoscope and its size and extent estimated. If local anaesthetic transurethral resection is appropriate (tumour <5 cm in diameter), the base of the tumour is injected under direct vision with a haemostatic local anaesthetic mixture using an Endoneedle. The mixture comprises 5 ml of 1% lignocaine and 5 ml of 1% lignocaine with adrenaline 1 in 200,000, giving a final concentration of adrenaline 1 in 400,000 (if further local anaesthesia is required 1% lignocaine plain 10–20 ml may be used). Following this the Integrated Cystoscope is removed, the urethra dilated to 26F with sounds, and a conventional resectoscope (24F) inserted. A standard resection of the bladder tumour is then performed, with care being taken not to overfill the bladder. Post-operative management is routine.

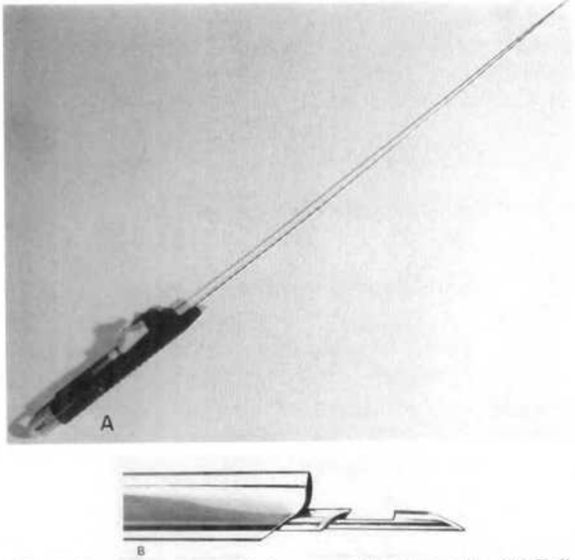


Fig. 1 Endo-cut automatic tissue core biopsy needle. (A) Full-length view. (B) Close-up showing biopsy needle emerging from the instrument channel of the Integrated Cystoscope.

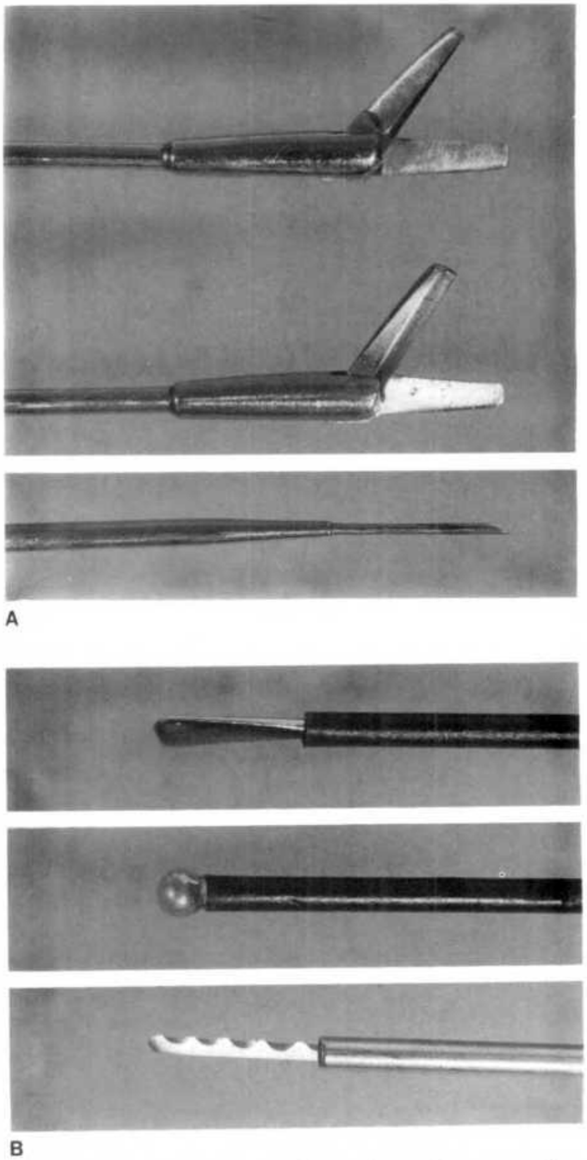


Fig. 2 (A) (Top to bottom) Endoscissors. Reverse cutting scissors. Endoneedle. (B) (Top to bottom) Electrosector. Diathermy probe (monopolar). Endoknife.

Vesicolithotomy

After initial cystoscopic assessment the stone is fragmented using a 5F electrohydraulic probe. The urethra is then dilated and the fragments evacuated via a resectoscope sheath.

Procedures—Bladder Neck and Prostate

Bladder neck incision

Anaesthesia of the bladder neck is achieved by injecting 1% lignocaine plain sub-trigonally via an Endoneedle into the areas on either side of the ureteric orifices (Fig. 3). The bladder neck and prostate are then infiltrated (Fig. 3) with 10 ml of the haemostatic local anaesthetic mixture described previously (additional analgesia may be achieved using 1% lignocaine plain). An insulated endoscopic needle (Electrotest-needle) has recently been designed. This enables injection of local anaesthetic and immediate testing of the adequacy of analgesia using an electrical stimulus generated from a diathermy machine. Following this the Electrosector (Fig. 2) is introduced via the Integrated Cystoscope and a standard bladder neck incision is performed. Further post-operative care is routine. In this instance the reduced calibre of the Integrated Cystoscope (17F) compared with a standard resectoscope (24–26F) enables the procedure to proceed with maximum patient comfort.

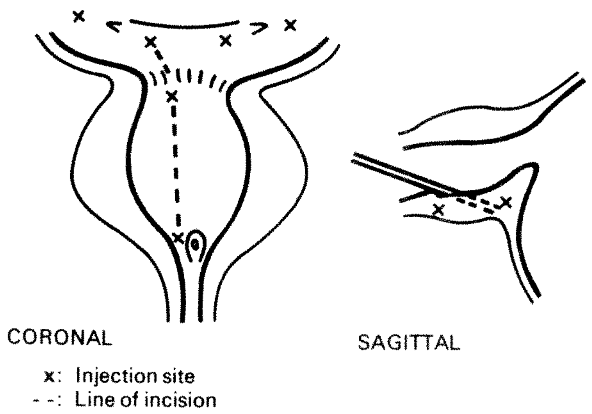


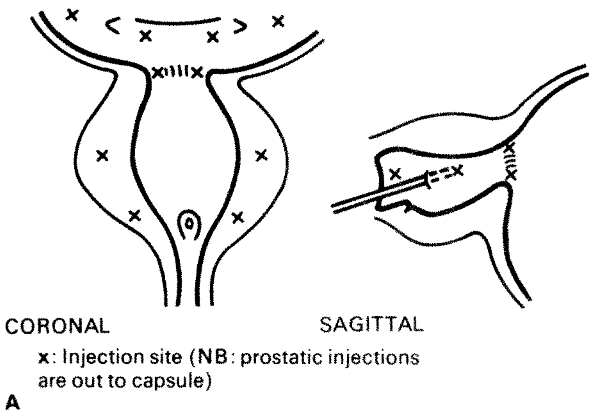
Fig. 3 Local anaesthetic injection sites. Bladder neck incision.

Transurethral resection of the prostate

Anaesthesia of the bladder neck and prostate is achieved as described above. Additional sites of injection are shown in Figure 4. It is important to inject the haemostatic local anaesthetic mixture to a depth sufficient to be close to the prostatic capsule if adequate pain relief is to be achieved. The urethra is then dilated with sounds and a standard transurethral resection performed using a conventional resectoscope. This method is best suited to prostates where the weight of resected material is estimated to be no more than 40 g. Whilst larger glands could be resected, limitations are imposed by the length of time for which a patient may be expected to remain comfortable whilst in the extended lithotomy position.

Prostatic biopsy

Following routine cystoscopy, biopsy of the prostate can be performed under direct vision using the Endocut automatic tissue core biopsy needle (Fig.


CORONAL
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x: Injection site (NB: prostatic injections are out to capsule)
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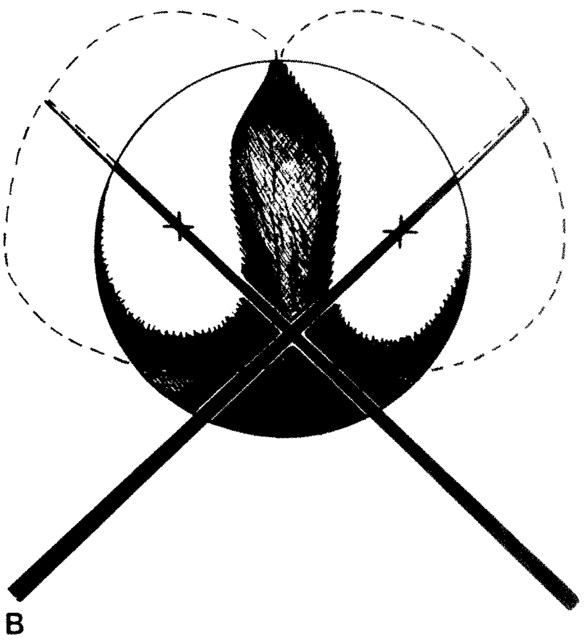

Fig. 4 Local anaesthetic injection sites. (A) Transurethral resection of prostate. (B) Depth of injection in prostate.

1) introduced via the instrument channel of the Integrated Cystoscope. The design of this needle enables single-handed operation, so that a firm hold can be maintained on the endoscope during the biopsy procedure.

Endoprostatic stent insertion

The Fabian Urospiral, a prostatic endoprosthesis for the relief of outflow obstruction, can be inserted under sedoanalgesia. At cystoscopy, prostatic urethral length is estimated using a graduated ureteric catheter. The correct size of Urospiral (Porges, UK) is then selected (prostatic length plus 15 mm), railroaded over the ureteric catheter and, using the Integrated Cystoscope, correctly positioned under direct vision.

Procedures—Urethra

Urethrotomy (male)

The urethra is instrumented with the Integrated Cystoscope and the stricture divided (at 6 or 12 o'clock) under direct vision using an endo-knife (Fig. 2) passed via the instrument channel of the cystoscope. Following release of the stricture, urethral dilatation to 24F is performed with antibiotic cover for 3 to 5 days. A urethral catheter is not routinely left *in situ* following the treatment of short, simple strictures.

Urethrotomy (female)

Following cystoscopy, the urethra is injected at 12 o'clock with 1% lignocaine delivered via an Endoneedle. Using reverse cutting scissors (Fig. 2) or an Otis urethrotome a urethrotomy to 35F is then performed.

Procedures—Ureteric

Ureteric catheterisation

A 5 to 7F ureteric catheter (or J stent over a guide wire) can be passed down the instrument channel of the integrated cystoscope and the ureteric orifice catheterised easily for the purposes of passing the stent or performing retrograde ureterography.

Removal of double-J stent

This is effected by means of 7F semi-rigid toothed grasping forceps under direct vision.

Ureteroscopy

Rigid ureteroscopy can be performed in the lower third of the ureter where the ureteric orifice has been previously dilated (J stent *in situ* or Teflon dilators). Ureterolithotomy using a 5F electrohydraulic probe can be carried out.

The Miniscope (Candela) has advantages over conventional rigid ureteroscopes in that its reduced size causes much less trauma and discomfort—ureteric dilatation being unnecessary (Watson, personal communication). Additional analgesia can be achieved by using a non-steroidal anti-inflammatory (suppository) given 30 to 60 min preoperatively.

Treatment of Ureterocele

Endoscissors or the Electrosector (Fig. 2) passed via the Integrated Cystoscope can be used to incise and deroof ureteroceles in adults.

Treatment of vesicoureteric reflux

Where appropriate, vesicoureteric reflux in adults can be managed by Teflon injection using a wide calibre Endoneedle in conjunction with a pressure syringe (Lewis Medical Ltd). This delivery system can provide effective Teflon injection at a fraction of the cost of currently available conventional equipment.

Open Procedures

Penile

Complete penile block can be achieved using a mixture of lignocaine 1% (15 ml) and bupivacaine 0.5% (15 ml). The base of the penis is injected initially in the mid-line and then laterally to each side. Circumferential infiltration of the ventral surface completes the block. In this fashion, circumcision, frenuloplasty, partial amputation and penile biopsy can be achieved without difficulty.

Scrotal

Fifteen ml of local anaesthetic mixture (see penile procedures above) can be injected directly into the spermatic cord on each side (for bilateral procedures) at the level of the scrotal neck. A further 5 ml of 1% lignocaine plain are then injected into the scrotal skin in the line of the intended incision. The anaesthesia so obtained is entirely adequate for a wide range of scrotal procedures—testicular biopsy, orchiectomy, vasectomy, epididymectomy, excision of epididymal cysts, hydrocele repair, testicular implantation and scrotal exploration for infertility.

In these procedures, as in the penile operations, the bupivacaine component of the anaesthetic block provides good post-operative pain relief for several hours. After the local block has worn off, further analgesia is provided by oral preparations such as paracetamol, co-proxamol, ibuprofen and mefenamic acid.

Flumazenil

The specific benzodiazepine antagonist flumazenil (Anexate, Roche, UK), in a dose of 0.5 mg administered as an intravenous bolus, is used in the following situations to effect immediate patient recovery:

(1) In elderly, sick patients where the termination of sedation is desirable to minimise potential post-operative complications.
(2) In day-case surgery (see Discussion).
(3) In cases of inappropriate sedation secondary to the use of midazolam. Such instances should be rare if midazolam is used appropriately (Birch and Miller, 1988).

Results

During the period September 1987 to January 1989, 1020 urological procedures, both endoscopic and open, were carried out using sedoanalgesic techniques. Patients ranged in age from 16 to 98 years with more than one-third being over 70 years of age and 16% American Society of Anesthesiologists grade III or IV, *i.e.* unfit for general anaesthetic day-case surgery using conventional criteria (Royal College of Surgeons of England, 1985).

Tables 1 to 3 detail the number of procedures carried out in each treatment category.

There have been no major respiratory or cardiovascular complications related to our use of midazolam during this time. The results in patients having transurethral resections of the prostate, bladder neck incisions and urethrotomies under local anaesthesia have been satisfactory and compare favourably with those obtained using conventional anaesthetic and instrumental techniques (Miller *et al.*, 1990). Over 150 local anaesthetic prostate resections have been performed to date. Analysis of the results obtained with the first 100 patients shows an improvement in flow rates from 8.5 to 24 ml/s, the average weight of prostate tissue resected being11.1 g. With experience, all prostates up to 40 g may be operated on using this technique. It is thus suitable for 60% of all glands coming to resection. Preliminary experience with the Fabian Urospiral in 21 patients is encouraging. Satisfactory results can be expected in 75 to 80% of patients presenting in acute retention or with symptoms of outflow obstruction. However, the success rate falls to 50% or less when patients present with chronic retention of urine. The Urospiral would thus seem to be an attractive option in selected patients, since its use can help to avoid the need for major surgery or urethral catheterisation.

Table 1 Procedures Performed using Sedoanalgesia

Endoscopic	893 (intervention rate 53%)
Open	127
Total	1020

Table 2 Endoscopic Procedures

Ureteric (n = 88)	*Vesical* (n = 83)	*Prostate/bladder neck* (n = 128)	*Urethra* (n = 176)
Catheterisation/retrograde 35	Bladder tumour	TURP 38	Urethrotomy (male) 76
J stent: removal 34	Resection 17	Prostatic biopsy 26	Urethrotomy (female) 81
insertion 14	Diathermy 19	Bladder neck incision	Diathermy caruncle 5
Ureteroscopy 2	Biopsy 33	Diathermy 54	Steroid injection 4
Deroofing ureterocele 2	Vesicolithotomy 13	Laser 6	Urethral dilatation 9
Ureterolithotomy 1	Suprapubic cystoscopy 1	Urospiral 4	Drainage abscess 1

Table 3 Open Procedures

Penile (n = 31)		*Scrotal* (n = 96)	
Circumcision	29	Bilateral orchiectomy	39
Glans biopsy	2	Hydrocele repair	8
		Vasectomy	29
		Testicular biopsy	10
		Exploration scrotum	2
		Epididymectomy	6
		Frenuloplasty	1
		Testicular implant	1

Discussion

Of the cases reported in this study, 816 (80%: endoscopic 719, open 97) were carried out on a day-case basis. Our experience with sedoanalgesia has shown it to provide a wide range of safety in patients independent of age and overall level of fitness (or ASA status). This is an important consideration in specialties such as urology, which have a significant proportion of elderly, unfit patients. Such subjects would not normally be considered suitable for general anaesthetic day-case surgery and would require conventional admission with its attendant inconvenience and increase in cost (Ogg, 1980).

The Royal College of Surgeons of England is seeking to encourage the practice of day-case surgery, which it regards as a cost-effective element in surgical care. It is estimated that 37% of all general surgical and urological procedures could be adequately performed on a day-case basis (Royal College of Surgeons, 1985). However, in many health regions this figure has not been achieved. Such is the case in the North East Thames Region, where the level of day-case general surgery/urology currently runs at 12% (North East Thames Regional Health Authority, 1988). The national figure (England) for urology—23% in 1987/88 (source DHSS)—also falls well short of estimated rates. This may be due, in part, to a reluctance of nursing staff, anaesthetists and surgeons to change established practices (Ward, 1988). Inadequate day-case facilities and an increasingly elderly population also militate against change.

The use of sedoanalgesia enables increased efficiency in a day-case situation. Theatre dynamics are improved, with little delay between cases and no need for the patient to spend time in recovery prior to return to the ward. These are important considerations when theatre time has been estimated to cost in the order of £400/h.

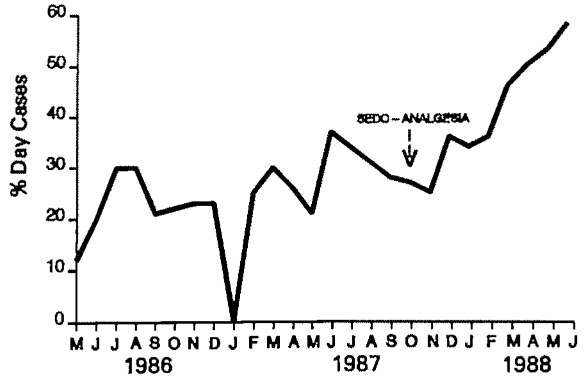

Fig. 5 Percentage of patients treated as day-cases at the Royal Northern Hospital between 1986 and 1988.

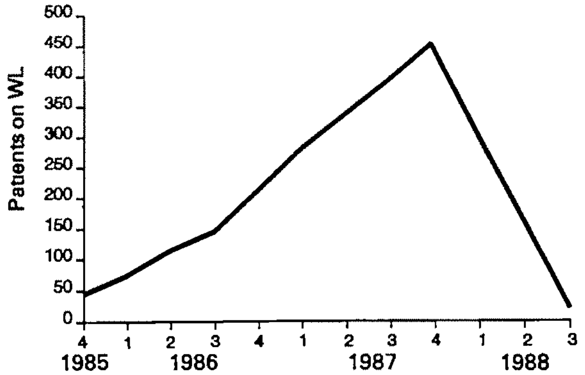

Fig. 6 Waiting list, Royal Northern and Whittington Hospitals 1985 to 1988. (Sedoanalgesia introduced in the third quarter of 1987).

In our practice the use of sedoanalgesia has increased the percentage of patients treated as day-cases from 25 to 60% (Fig. 5). This, in turn, has resulted in a dramatic reduction in the size of the waiting list (Fig. 6). The potential of day-case surgery to reduce waiting lists has been mentioned by others (Ogg, 1980; Royal College of Surgeons of England, 1985) and the financial and social implications of adopting such a policy are self-evident.

Benzodiazepines can safely provide anxiolysis, amnesia and sedation. They are thus suitable agents for premedication. However, the use of drugs for premedication in day-case surgery is controversial and they are often omitted in the belief that they will adversely affect the quality and duration of recovery following brief ambulatory procedures (Ogg, 1980; Shafer *et al.*, 1989). This is despite the fact that they increase patient tolerance of surgery, especially where this is to be performed under local anaesthesia. In this setting, midazolam has advantages over diazepam through its lack of tissue irritation, shorter duration of action (1–3 h), profound antegrade amnesia and excellent uptake following intramuscular administration (Dundee *et al.*, 1984). Our experience is that most patients are subjectively fit for discharge 1 h post-operatively. However, at least 20% of patients take longer than this to recover (Birch *et al.*, 1990a). This percentage is higher if more sensitive tests of recovery are used (Birch *et al.*, 1990b).

The introduction of the specific benzodiazepine antagonist flumazenil has, to a large extent, eliminated problems related to prolonged patient recovery following single-dose sedation techniques which use a benzodiazepine. Flumazenil will completely reverse the psychomotor effects of benzodiazepines within 1–2 min of intravenous injection (Brogden and Goa, 1988). In a pilot study (84 patients), we have shown that its use enabled 83% of patients to recover and be potentially fit for discharge within 15 min of surgery (control group 23%) ($P<0.001$) (Birch *et al.*, 1990a).

Given concern over the possibilities of resedation following the use of flumazenil (elimination half-life approximately 60 min), patient recovery profiles were assessed in a second study of 44 patients.

Using a battery of psychomotor tests it was shown that flumazenil (0.5–1.0 mg intravenously) was both efficacious and without evidence of resedation in a 6-h test period (Birch *et al.*, 1990b). Its use improves patient cooperation in the post-operative period, with a subsequent reduction in demands on nursing care both in theatre and on the ward. The potential for enhanced discharge also allows for the optimal use of beds and theatre time. This is important where day-case facilities are limited by restrictions in nursing staff (Silver, 1989), the availability of beds or their provision in the setting of a conventional ward (Birch *et al.*, 1988). The complementary use of midazolam and flumazenil in this situation can improve efficiency. This same combination also proves efficacious where midazolam is administered intravenously immediately prior to surgery. Such a technique enables patients to walk into theatre before surgery and to leave immediately after operation. Preliminary results in 50 patients undergoing scroto-genital surgery show this technique to have a significantly lower morbidity rate than conventional general anaesthesia.

It is to be noted that our use of flumazenil has not been associated with arousal or anxiety phenomena, as reported by some authors (Brogden and Goa, 1988). This is probably due to the fact that patients are not awakening in a strange environment, that chronic users of benzodiazepines are excluded from receiving flumazenil, and that most procedures are not very painful *per se*. Where pain might be expected to complicate the post-operative course (scrotal/penile operations), the use of local anaesthetic blocks ensures a comfortable, pain-free recovery.

Whilst a major use of sedoanalgesia is for day-case procedures, it is also suitable for in-patient surgery. It might be argued that where conventional admissions are concerned and time not a limiting factor, general anaesthesia or regional anaesthetic techniques are appropriate. However, the safety of sedoanalgesia is an important consideration in the age group concerned. General anaesthesia and regional techniques are not without problems in patients with pre-existing pulmonary and cardiovascular disease. Such procedures may also be technically difficult and time-consuming. In unfit and elderly patients, the termination of sedation following the completion of surgery is desirable if complications are to be minimised. The use of midazolam and flumazenil enables this to be achieved.

Midazolam has no analgesic properties and pain relief should be achieved by the use of adequate local anaesthesia. It is not acceptable merely to sedate patients heavily. It is the anxiolytic properties of midazolam combined with reduced sensory awareness which the surgeon should be seeking to exploit. Amnesia can be regarded as a useful additional component of the drug's action, not an excuse to ablate the memory for otherwise unacceptable surgical procedures.

There is no doubt that sedoanalgesia has radically changed the practice of urology. Safety, efficiency and cost-effectiveness coupled with patient preference combine to make sedoanalgesia a preferable alternative to general anaesthesia for many urological procedures, both endoscopic and open.

Acknowledgements

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The Authors

B. R. P. Birch, MA, MB, FRCS, Lecturer in Urology, Institute of Urology.

K. M Anson, MB, BS, Senior House Officer, Royal Northern Hospital.

R. A Miller, MS, MB, FRCS, Consultant Urologist and Postgraduate Dean, Royal Northern Hospital.

Requests for reprints to: B. R. P Birch, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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Calcium Oxalate Crystallisation Kinetics and the Effects of Calcium and γ-Carboxyglutamic Acid

S. NISHIO, J. P. KAVANAGH, E. B. FARAGHER, J. GARSIDE and N. J. BLACKLOCK

Department of Urology, University Hospital of South Manchester, Manchester

Summary—γ-carboxyglutamic acid (GLA) is an amino acid with a high affinity for calcium. It is found in urine both as the free amino acid and incorporated into proteins such as osteocalcin. Free and bound GLA have been reported to be found at higher concentrations in the urine of stone formers than controls. We have investigated the effect of GLA and calcium, at physiological levels, on the crystallisation of calcium oxalate using a mixed suspension mixed product removal continuous crystalliser.

GLA caused very significant changes in the crystallisation kinetics, but the effect was dependent on the calcium concentration. At 4 mM calcium, GLA decreased the growth rate and increased the nucleation rate; at 12 mM the reverse occurred. At all concentrations of calcium tested, GLA caused a significantly increased crystal mass to be produced. Our evidence supports the hypothesis that GLA modifies calcium oxalate crystallisation and could be a promoter of stone formation *in vivo*, particularly at moderately elevated levels of calcium excretion.

Many studies, using different methodologies, have been carried out to investigate the effects of modifiers of calcium oxalate crystallisation *in vitro*. Mixed suspension mixed product removal (MSMPR) continuous crystallisers have been used frequently because they are good models for renal precipitation and can give quantitative results for crystal growth and nucleation rates (Finlayson, 1972; Miller *et al.*, 1976; Rodgers and Garside, 1981). Such systems have been used to examine the effects of oxalate, magnesium, citrate, pyrophosphate, RNA and some urinary macromolecules (Drach *et al.*, 1982; Li *et al.*, 1985; Robertson and Scurr, 1986; Kohri *et al.*, 1988, 1989).

The effect of varying calcium concentrations in artificial urine in an MSMPR system has not been systematically investigated. This is also true for many urinary constituents normally present in low concentrations, but which might nevertheless be significant modifiers of calcium oxalate crystallisation. There is evidence that one of these, γ-carboxyglutamic acid, might be implicated in renal stone formation.

GLA is an amino acid produced by post-translational carboxylation of glutamic acid in proteins such as prothrombin and osteocalcin and is responsible for their strong calcium binding activity (Fig. 1). In the presence of calcium the GLA residues allow specific conformational changes and promote osteocalcin binding to hydroxyapatite (Fig. 1) (Lian and Gundberg, 1988). GLA is excreted in the urine both as the free amino acid and in undegraded GLA containing proteins, especially osteocalcin (Shah *et al.*, 1978; Lian and Gundberg, 1988). The mean urinary concentration of free GLA has been reported to be 35 or 68 µmoles/day (Fernlund, 1976; Joost *et al.*, 1981). Elevated concentrations have been found in the urine of recurrent calcium oxalate stone formers, nephrocalcinosis and primary hyperparathyroidism patients (Resnick *et al.*, 1980; Joost *et al.*, 1981). Furthermore, the presence of osteocalcin in calcium containing renal calculi and paediatric bladder stones has been reported (Lian *et al.*, 1977; Ogasawara *et al.*, 1987).

These findings are suggestive of a role for GLA in calcium oxalate lithiasis but do not provide any evidence for a direct activity as a modifier of

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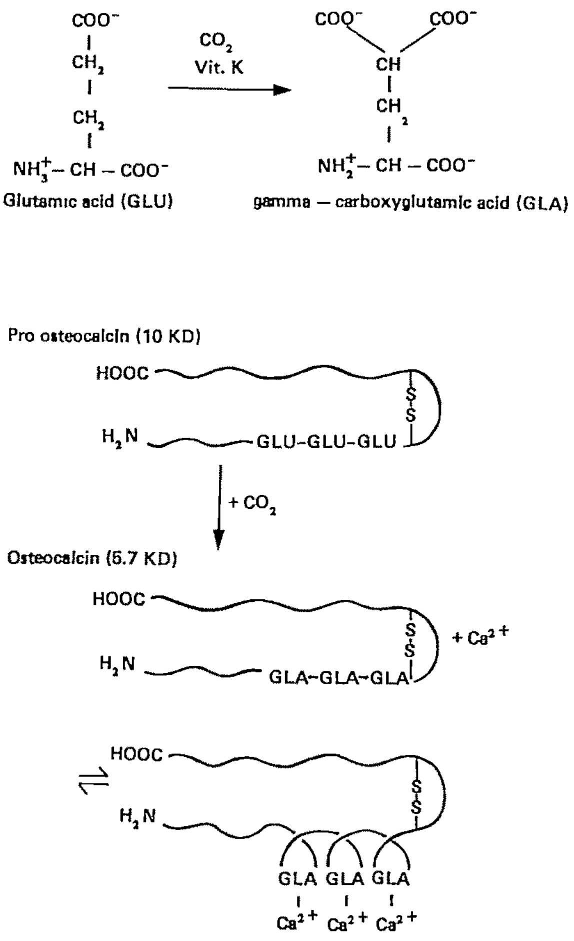

Fig. 1 Structure of GLA and its role in binding calcium to osteocalcin.

calcium oxalate crystallisation or stone formation. We have therefore investigated this effect and how this is influenced by calcium, using artificial urine in an MSMPR continuous crystalliser.

Materials and Methods

We used a miniature MSMPR system. The crystallisations were carried out in a water jacketed vessel maintained at 37°C with a volume of 20 ml. Three feed solutions (I, II and III) were pumped into the crystalliser by a Technicon proportioning peristaltic pump which was also used to withdraw the mixed product via a constant level device. Air bubbles were introduced into each line at 2-s intervals to prevent electronic noise transmission from the pump and the suspension was stirred by a magnetic flea. Full details of this system are presented elsewhere (Nishio *et al.*, 1989).

The final composition of the simulated urine was essentially the same as that used by Kohri *et al.* (1988). Solution I contained GLA and sodium salts of oxalate, phosphate, citrate and chloride. Solution II contained calcium chloride and solution III the remaining ingredients (Table 1).

The solutions were pumped at rates of 0.11, 0.11 and 2.85 ml/min to give the final composition shown in Table 2 and a residence time of 6.8 min. In the final mixture, calcium was varied between 4 and 12 mM, oxalate was fixed at 0.6 mM and GLA, when present, was used at 25, 50 or 75 μM.

The feed solutions consisted of analytical grade reagents dissolved in distilled water and were filtered through 0.22 μm Millipore filters. GLA was supplied by the Sigma Chemical Co. (DL-gamma carboxyglutamic acid).

Particle size distributions were analysed with an Elzone (80XY) particle counter and transformed to a log particle numbers/linear diameter distributions. In all runs the data points lying between crystal size of 9 and 14 μm were fitted by linear regression to a straight line and the growth rate (G, μm/min), nucleation rate (B_O, no/min/ml) and suspension density (M_T, mg/l) (assuming a calcium oxalate crystal density of 2.22 g/cm^3) were calculated. A full description rate of theoretical and practical aspects is given by Rodgers and Garside (1981). The range of crystal sizes examined in this study was slightly smaller than previously because at low concentrations of calcium not enough large size crystals were produced for accurate measurement to be made. The crystal size distribution was measured about every 8 min until 56 min had elapsed, at which time the size distribution had reached a steady state. Following this point, removed product was collected and filtered (0.2 μm Millipore filters) for scanning electron microscopy (SEM).

Each experiment was performed in quadruplicate with multiple particle size distribution analyses from 56 min onwards, limited only by reagent volume or blockage of the 150 μm orifice tube.

The significance of the results was judged by analysis of variance after suitable transformation of results to give normally distributed data (Aitken *et al.*, 1989). The analysis of variance evaluated the interactions between calcium and GLA levels as well as their separate effects. Logarithmic transformations were used for growth rate and suspension density and a fourth root transformation for nucleation rate. Because the number of replicates

Table 1 Recipe for Feed Solutions

Feed solution I	*(g/l)*	*Feed solution II*	*(g/l)*	*Feed solution III*	*(g/l)*
$NaH_2PO_42H_2O$	86.63	$CaCl_2 \cdot 2H_2O$	14.99 to 44.97	Na_2SO_4	3.26
Na_2HPO_4	11.08			$MgSO_4 \cdot 7H_2O$	1.87
$Na_3C_6H_5O_7 \cdot 2H_2O$	14.90			NH_4Cl	2.52
NaCl	172.10			KCl	6.59
$Na_2C_2O_4$	2.05			Sodium lauryl sulphate	0.02
γ-carboxyglutamic acid	0 to 0.365				

Table 2 Composition of Artificial urine in Final Mixture

Substance	*Concentration (mmol/l)*
Na	171.1
Mg	7.0
K	81.5
Cl	258 0
NH_4	43.5
SO_4	28.1
PO_4	24.9
Citrate	2.0
Ca	4.0 to 12.0
Oxalate	0.6
γ-carboxyglutamic acid	0 to 0 075

was not identical for each calcium/GLA combination, the order in which the factors were fitted into the model affects their significance. Separate ANOVA tables were thus developed, fitting calcium first and then GLA first. There was very little difference between the 2 sets of tables; fitting calcium first gave slightly higher F-ratios and these are the results shown in Table 3.

The analysis of variance divides the variation in the measurements into components due to each of the experimental factors and a residual (unaccounted for) component. The F-ratios are constructed from the variance components and estimate the statistical significance of the influencing factors. The higher the F-ratio, the greater is the influence of the factor on the outcome of the experiment.

Table 3 F-Ratios from Analysis of Variance Tables

	F-Ratio (degrees of freedom) (P)		
Source	*G*	B_O	M_T
Calcium	16 (2) (<0.001)	183 (2) (<0.001)	366 (2) (<0 001)
GLA	11 (3) (<0.001)	7 (3) (<0 001)	7 (3) (<0.001)
Calcium + GLA	13 (6) (<0.001)	10 (6) (<0.001)	4 (6) (0.001)

Results

The analysis of variance showed that very significant changes in growth rate, nucleation rate and suspension density were associated with changes in calcium and GLA concentrations. There was also a significant interaction between calcium and GLA, indicating that the effect of adding GLA differed according to the calcium concentration being used (Table 3). The most dramatic response (largest F-ratio) was the increase in suspension density with increasing calcium concentration. This was brought about by an increase in nucleation rate and accompanied by a slight fall in growth rate (Table 4, Fig. 2). Compared to the effects of calcium, the response to GLA and the interaction between these 2 was much smaller (the F-ratios are much smaller, Table 3).

GLA at 4 mM calcium brought about a decrease in growth rate and an increase in nucleation rate. At 12 mM calcium this pattern was reversed and

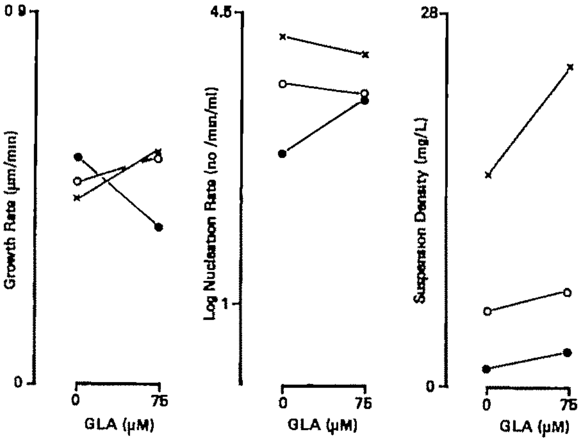

Fig. 2 The effect of GLA on calcium oxalate crystallisation at 4 mM (●), 8 mM (○) and 12 mM (×) calcium.

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Table 4 Results for Kinetics of Crystallisation for Different Calcium/GLA Combinations

			GLA (μM)			
		Control	*25*	*50*	*75*	*P**
Ca 4mM	G (μm/min)	0.55	0.47	0.39	0.38	<0.001
	B_O (no/min/ml)	692	2954	2786	2909	<0.001
	M_T (mg/l)	1.62	4.28	2.30	2.37	<0.001
Ca 8mM	G (μm/min)	0.49	0.52	0.46	0.55	<0.001
	B_O (no/min/ml)	4433	4556	7094	3292	0.004
	M_T (mg/l)	7.42	9.16	10.12	7.65	0.172
Ca 12mM	G (μm/min)	0.45	0.52	0.50	0.56	<0.001
	B_O (no/min/ml)	15890	11111	11591	10419	0.019
	M_T (mg/l)	21.86	23.21	21.42	26.96	0.040

*Refers to the probability that the results with GLA are equal to the control results.

GLA caused an increase in growth rate and a fall in nucleation rate. The suspension density was increased by GLA at all calcium concentrations. There was little difference to be seen between the different concentrations of GLA (Table 4) and interpretation of the results is simplified if they are considered as the effect of calcium, with or without added GLA; Figure 2 shows, as an example, the effect of 75 μM GLA.

Scanning electron microscopy of the crystals showed that in control experiments mainly calcium oxalate trihydrate crystals were formed. When GLA was present the main crystal form was again the trihydrate but there were also many aggregates formed of large numbers of small crystals (Figs 3 and 4).

Discussion

We have introduced some experimental variations from previous MSMPR studies (Li *et al.*, 1985; Kohri *et al.*, 1988, 1989). These are the use of a miniature crystalliser (20 ml) and the use of 3 feed solutions with unequal flow rates instead of the usual 2 at equal flow rates. The high cost of synthetic GLA would have prohibited the use of a 200 ml crystalliser and 3 feed solutions were used for

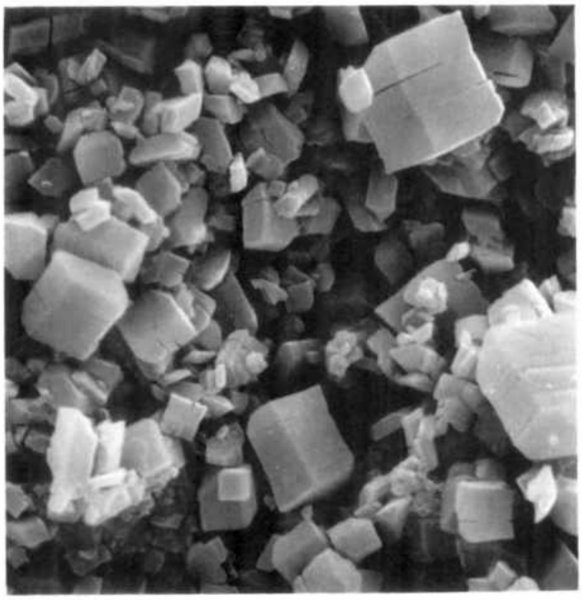

Fig. 3 SEM of calcium oxalate crystals recovered from a control experiment at 4 mM calcium.

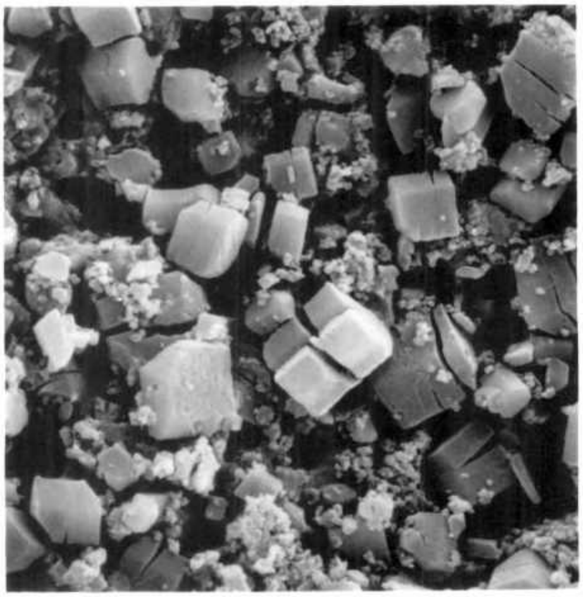

Fig. 4 SEM of calcium oxalate crystals recovered from an experiment in which GLA was included at 50 μM (calcium = 4 mM).

consistency with "approximately whole urine" experiments, which will be reported later. An important factor in MSMPR methodology is that the product removed should be representative of the slurry from which it is taken. This was checked in our system using 14 μm latex beads. Experiments with a variety of calcium and oxalate concentrations, using the same synthetic urine mixture and residence time as used previously (Kohri *et al.*, 1988), gave very similar results in the 20 ml crystalliser to those found using a 200 ml system (Nishio *et al.*, 1990).

The concentrations of calcium (4–12 mM) and oxalate (0.6 mM) which we used are at the upper end of, or slightly above physiologically normal levels in urine, but lower than has often been used by others. A practical limitation is the need to generate a sufficient crystal density for valid results to be obtained. To some extent we have overcome this problem by many repeated measurements and comprehensive statistical analysis.

The result of increasing calcium in the absence of GLA was a very significant increase in crystal mass. Taking this into account, it is possible to calculate the amount of calcium and oxalate in solution and thus the supersaturation ratio (using EQUIL2) (Werness *et al.*, 1985). These were 11, 18 and 19 at 4, 8 and 12 mM calcium respectively. The small decrease in growth rate which we observed with increasing calcium concentration does not fit with the generalisation of growth rate increasing with calcium oxalate supersaturation (Kohri *et al.*, 1988). It is possible that some calcium phosphate crystallisation may be occurring, although we have no SEM evidence for this. At calcium concentrations in excess of 12 mM we did find higher growth rates, in keeping with Figure 5 of Kohri *et al.* (1988).

When GLA at physiological concentrations was included in the synthetic urine it increased the total mass of crystals produced, although its effects on growth rate and nucleation rate were dependent on the calcium concentration.

The nature of calcium/GLA interactions has not been analysed or quantified. It is possible that complexes form in which calcium is locally concentrated (at the molecular level) so that calcium oxalate can more easily exceed its formation product, giving rise to an increase in nucleation rate. The associated decrease in growth rate may result from saturation relief. On the other hand, at high concentrations of calcium (12 mM) and at the levels of GLA used, the proportion of calcium associated with GLA might no longer be significant and GLA may enhance growth rate by aggregation mechanisms. The electron microscopy results support the idea that aggregation phenomena are a feature of the modifying action of GLA on calcium oxalate crystallisation.

Previously reported studies concerning urinary GLA and GLA containing proteins have not always arrived at the same conclusions. Nakagawa *et al.* (1983) purified a glycoprotein inhibitor of calcium oxalate crystallisation which contained GLA. As a calcium binding agent it is reasonable to suppose that GLA would act as an inhibitor because it would tend to lower the calcium oxalate supersaturation, in a similar way to other inhibitors such as citrate or glutamic acid (Azoury *et al.*, 1986). However, at the low physiological concentrations of GLA, effects on the supersaturation ratio may be insignificant. Evidence of elevated levels of urinary GLA in stone formers and hyperparathyroid patients and the presence of osteocalcin in calcium stones (Lian *et al.*, 1977; Resnick *et al.*, 1980; Joost *et al.*, 1981; Ogasawara *et al.*, 1987) suggest that GLA could be a promoter of calcium oxalate crystallisation and it has been reported that urine from primary hyperparathyroid patients has a promotive effect on calcium oxalate crystallisation (Koide *et al.*, 1988).

Our MSMPR results provide the first evidence for a direct activity of GLA as a modifier of calcium oxalate crystallisation and are supported by the SEM results. The consistent increase in suspension density supports the hypothesis that GLA is a promoter of stone formation. This increase in crystallisation is more likely to enhance the chance of urolithiasis when it is brought about by an increased growth rate than by an increase in nucleation rate, and this is the effect of GLA at the higher calcium concentrations tested. It is therefore possible that GLA, even at physiologically normal concentrations, may amplify the risk of stone formation associated with above average calcium excretion. However, it should be remembered that results obtained using artificial urine might be modified for real urine by macromolecules or other substances.

Although we could not examine the *in vitro* effects of osteocalcin or urinary GLA containing protein, it might be expected that these would have similar or more significant effects on calcium oxalate crystallisation, since they might facilitate more GLA-calcium complexes as nucleation sites, or the protein might provide a backbone of independent nucleation sites which may grow together into a large aggregate.

Further studies on the effect of GLA binding protein on calcium oxalate crystallisation are necessary. It will also be necessary to analyse quantitatively free GLA and GLA binding protein in urine stone formers and normal controls.

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The Authors

S. Nishio, MD, Lecturer, Department of Urology, Ehime University, Japan.

J. P Kavanagh, PhD, Principal Biochemist, Department of Urology, University Hospital of South Manchester.

E. B. Faragher, Medical Statistician, University Hospital of South Manchester.

J. Garside, DSc, FIChemE, Professor of Chemical Engineering, University of Manchester Institute of Science and Technology.

N. J. Blacklock, FRCS, Professor of Urology, University Hospital of South Manchester.

Requests for reprints to: J. P Kavanagh, Department of Urology, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR.

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Chronic Dehydration Stone Disease

O. M. EMBON, G. A. ROSE and T. ROSENBAUM

St Peter's Hospitals and Institute of Urology, London

Summary—A study was made of 819 patients attending a metabolic stone clinic. A firm diagnosis was made in 708 (86%) and in 132 of these (19%) the diagnosis was thought to be chronic dehydration. The records were available for study for 87 males and 11 females in the chronic dehydration group. The mean age at presentation was 43 years. The causes of chronic dehydration were hot climate (62%), with hot occupation and low water intake almost equal in second place. In patients with a single cause of chronic dehydration, 57% also had a dietary risk factor for urolithiasis and this was most commonly high oxalate intake.

Following dietary advice, the mean urinary volume increased from 1720 to 2475 ml/24 h. This was accompanied by a rise in mean urinary calcium from 6.02 to 6.96 mmol/24 h, presumably due to the calcium in the additional water drunk. Urinary oxalate did not change significantly. The mean follow-up time was 4.85 years and the stone recurrence rate was low.

It was concluded that chronic dehydration is a common cause of urolithiasis; this can be treated satisfactorily by increasing water intake plus dietary advice in certain cases.

In recent years much effort has been directed towards investigation of the metabolic abnormalities involved in renal stone disease. One salient point is that 24-h urinary volume is the most important biochemical risk factor, being more important than either oxalate or calcium excretion (Robertson *et al.*, 1981). This is not surprising, since urinary volume affects the concentration of both oxalate and calcium, so that its affect is proportional to the second power of the volume.

The early evidence that chronic dehydration induced urolithiasis was reviewed by Rose (1968). Since then it has been shown that beach life-guards (Better *et al.*, 1978) and marathon runners (Milvy *et al.*, 1981) have a high incidence of urolithiasis. Ferrie and Scott (1984) noted that hot metal workers in Scotland had a high incidence of urolithasis but were unsure whether to blame exposure to the metals or the heat. Reports that high water intake actually prevents urolithiasis are very few. A notable exception was the prospective trial by Frank and de Vries (1966), which showed that education of those at risk of chronic dehydration led to a rise in urinary volume and a fall in the incidence of urolithiasis. However, Ljunghall *et al.* (1988) treated patients with idiopathic calcium nephrolithiasis with high water intake only and failed to achieve any marked reduction in stone recurrence rate. Possible reasons for this will be discussed below.

The frequency with which stone formation is due to chronic dehydration is not well known. Most authors fail to mention low urinary volume in their lists of the causes of urinary stones. A notable exception was a previous study from these hospitals (Rose, 1982) which found that chronic dehydration was the cause of stones in 13% of patients attending a metabolic stone clinic. This study has now been extended and the follow-up period considerably increased. It was therefore thought appropriate to review the results.

Patients and Methods

The records of 819 patients studied in the metabolic stone clinic in the last 20 years were reviewed. The following criteria were used to make the diagnosis of chronic dehydration stone disease:

1. Clearly defined history of exposure to heat due to climate and/or occupation, or of poor water drinking.

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2. Normal results on urinary and plasma samples.
3. History and/or radiology to exclude stone formation prior to exposure to heat and after exposure to heat.

Studies were performed on an out-patient basis. Patients were asked to bring with them at their first attendance a complete 24-h urine collection, *i.e.* before they had been given any medical advice at the clinic or questioned about diet or drinking habits. It was hoped thereby to obtain samples representative of their normal habits. They were also asked, in more recent years, to provide during each visit a further urinary sample to be used for crystal studies. Each patient was questioned about his occupation, periods of time in hot climates, and food and drink intake with special emphasis on foods rich in calcium and oxalate. The mean plasma and urinary values for each parameter were calculated for each patient using the pre-treatment values. The mean of these mean values was then calculated for each parameter. In addition, the means of all results were calculated. Each patient was asked to return for regular follow-up appointments with 24-h urine collections and for urinary crystal studies and annual plain X-ray films of the renal tract. The means of the 24-h urine collections taken after receiving advice at the clinic were also calculated in 2 ways.

Plasma and urinary analyses were measured by standard routine laboratory methods. In particular, urinary calcium was measured by flame photometry (emission in early years; atomic absorption in later years). Urinary oxalate has been measured extensively only since 1973, at first by oxalate decarboxylase (Hallson and Rose, 1974) and later by the continuous flow oxalate oxidase method (Kasidas and Rose, 1985).

Random samples of urine were examined for crystals with and without evaporation to standard osmolality by methods previously described (Hallson and Rose, 1976, 1978, 1988).

The X-ray films and the radiologists' reports were examined for evidence of stone formation during the follow-up period.

Patients with a diagnosis of urolithiasis due to chronic dehydration were given both verbal and written advice on how to increase 24-h urinary volume to 3:1. They were also advised to reduce any large dietary intake of calcium or oxalate.

Results

Of the 819 patients, it was possible to make a firm diagnosis in 708 (86%). Failure to make a diagnosis was because the patient failed to attend sufficiently often, the type of stone was not identified, borderline primary hyperparathyroidism was present (and neck exploration had not been performed) or other causes. The diagnoses in the 708 patients are given in Table 1; 132 (19%) were thought to have chronic dehydration stone disease and it was possible to review the records of 98 patients (87 males and 11 females). The mean age at presentation was 43 years (SD 11).

The mean values for 24-h urine collections from patients with chronic dehydration were normal. In particular, the value for calcium was 6.3 mmol/l (SD 2.3), urate 4.0 (SD 1.5), magnesium 4.8 (SD 2.0), oxalate 0.28 (SD 0.10), citrate 2.15 (SD 1.26) and pH 6.23 (SD 0.76). These values are similar to those found in this laboratory from 83 male doctors in the London area (Rose and Westbury, 1979). The mean plasma values were also normal according to reference values in this laboratory. The mean value for calcium was 2.40 mmol/l (SD 0.10), creatinine 0.09 (SD 0.02), inorganic phosphate 0.90 (SD 0.20) and urate 0.34 (SD 0.08).

Analyses of the risk factors for urolithiasis are shown in Tables 2 and 3. It can be seen that a single cause of dehydration was identified in 62% of the patients and in this group hot climate was the most frequent single cause, with hot occupation and poor water drinking virtually equal second. In the 61 patients with a single cause of dehydration only 43% had no dietary risk factor for urolithiasis. In the remaining 57% the most frequent dietary factor was high oxalate intake, with high calcium intake

Table 1 Incidence of Diagnosis

Cause	*No. of patients*		*(%)*	
Idiopathic hypercalciuria	230		32.5	
Chronic dehydration	132		18.6	
Medullary sponge kidney	95		13.4	
Urinary tract infection	52		7.3	
Primary hyperparathyroidism	41		5.8	
Cystinuria	28		4	
Uric acid stones	26		3.7	
High dietary oxalate	26		3.7	
Renal tubular acidosis	21		3	
Secondary hyperoxaluria	13		1.8	
Mild metabolic hyperoxaluria	8	28	1.1	3.9
Primary hyperoxaluria	7		1	
Miscellaneous (immobilisation, gout, Paget's disease)	29		4.1	
	708		100	

playing a less frequent role. Table 4 shows that similar patterns applied to the dietary risk factors in other causes of dehydration. A significant number of patients were exposed to more than 1 cause of dehydration (Table 2).

In one-third of the 81 patients with a history of exposure to a hot environment a definite period of exposure was identified, varying from 1 month to 40 years (mean 8.15 years). The delay from this initial exposure to the onset of first symptoms varied from a few weeks to 30 years (mean 14.6 years). The interval between the onset of symptoms and their first visit to our out-patient clinic varied from 1 month to 30 years (mean 8.9 years).

Table 2 Causes of Chronic Dehydration in 98 Stone Formers

	Hot climate	*Hot occupation*	*Poor water*	*Sport*	*Total*
Hot climate	24	15	16	2	57
Hot occupation	15	18	7	2	41
Poor water intake	16	7	17	2	40
Sport	2	2	2	2	5
Total	57	41	40	5	

Table 3 Risk Factors for Chronic Dehydration Urolithiasis

		Dietary risk factors			
Cause of dehydration		*Nil*	*OXD*	*CaD*	*Both*
Total with hot climate	54	22	19	6	7
Total with hot occupation	41	22	10	4	5
Total with poor water	40	13	20	0	7
Hot climate alone	24	11	8	5	0
Hot occupation alone	18	10	3	3	2
Poor water drinking	17	5	11	0	1
Sport alone	2	0	1	0	1
Totals	61	26	23	8	4
Hot climate and occupation	11	5	3	1	2
Hot climate and poor water	12	4	5	0	3
Hot occupation and poor water	7	3	3	0	1

The mean chemical composition of the urine and plasma samples was within normal limits (Gill and Rose, 1985). The mean values for 24-h urinary volumes and the content of calcium and oxalate before and after water drinking are shown in Table 4. The 2 methods of calculation give substantially similar results and to simplify matters only the mean of the means has been used from here onwards. It is seen in Table 4 that the mean 24-h urinary volume rose by 44%, calcium by 15.6% and oxalate by 8.6% (not significant) following advice on water drinking.

Stones were analysed from 56 patients; 42 were virtually pure calcium oxalate and a further 11 showed over 70% of calcium oxalate, with the remainder being calcium phosphate. One stone was a mixture of uric acid and calcium oxalate and 2 were mainly calcium phosphate. A total of 39 patients attended for a period of 1 year or more. The distribution of follow-up times is shown in Figure 1. The mean follow-up time was 4.85 years, the median 4.5 years, and the maximum 13 years. Of the 98 patients whose notes were studied only 7 were known to have stone recurrence or growth during follow-up. In 3 of these cases the patients had failed to re-attend for 2, 5 and 7 years respectively until they presented again with minor stone growth, major stone growth and colic due to a new stone respectively. In 3 other patients the increase in existing stones was very small, although definite, over periods of 3 and 10 years. In the remaining case there was clear stone growth for no obvious reason, although this patient did undergo

Table 4 24-h Urine Volume, Calcium and Oxalate Before and After Advice

	Before advice		*After advice*		
	No	*Mean*	*No*	*Mean*	*P*
Volume					
Mean of all 24-h urine samples	87	1781 (795)	254	2541 (896)	>0.005
Mean of means for each patient	60	1720 (751)	55	2475 (755)	>0.005
Calcium					
Mean of all 24-h urine samples	82	6.16 (2.43)	242	7.35 (2.78)	>0.005
Means of means for each patient	60	6.02 (2.34)	55	6.96 (2.19)	>0.005
Oxalate					
Mean of all 24-h urine samples	66	0.262 (0.099)	244	0.285 (0.088)	N.S.
Mean of means for each patient	52	0.269 (0.099)	56	0.292 (0.062)	N.S.

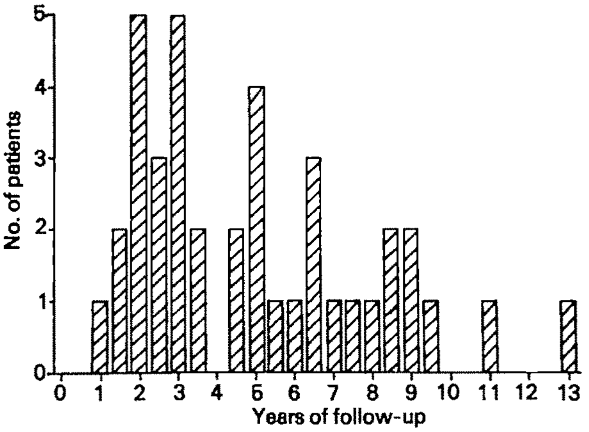

Fig. 1 Distribution of follow-up times in 39 patients with chronic dehydration.

a pregnancy and urinary infections during this period. The stone proved to be 56% calcium phosphate, 18% calcium oxalate and 2% magnesium ammonium phosphate, so that urinary infection could have played a part. The mean 24-h urinary volumes before and after advice on drinking in these 7 patients were 1423 and 2070 ml respectively, being considerably lower than the means for the whole group (Table 4).

In 38 patients there were sufficient data to compare the osmolality of the random urine samples before and after advice on drinking. The mean values before and after were 568 mosmol/kg (SD 201) and 514 (SD 173) respectively. Using a paired *t* test for the mean values this difference was not statistically significant, but nevertheless there were trends which seem to be important. Thus the number of patients with osmolarities above 700 mosmol/kg fell from 10 before advice to 5 after advice, while the number with osmolarities below 250 mosmol/kg rose from 1 to 4 patients. Inspection of the regression line in Figure 2 shows that patients with the highest urinary osmolality before advice showed the greatest falls after advice.

Discussion

The diagnoses listed in Table 1 are probably fairly representative of the stone population at large, except that urinary tract infection may be under-represented and cystinuria, renal tubular acidosis and hyperoxaluria slightly over-represented because of the particular interests of the clinic. Chronic dehydration appears as the second most common cause of stones and we suspect that this is true for the stone population of this country as a whole, although we have no way of proving this. It was confirmed that these patients showed no shift from the normal values of their plasma and urinary biochemical measurements.

Table 2 shows that a hot climate was the most frequent cause of chronic dehydration, being the sole cause in 24/98 patients. The next most frequent single cause was poor water intake (16 cases), but a hot occupation was a good third (15 cases). However, more than 1 cause of chronic dehydration was identified in 41 of the 98 cases. Thus 33/57 patients exposed to a hot climate showed another cause of dehydration, this being poor water intake in 16, hot occupation in 15 and sport in 2.

Not all patients exposed to chronic dehydration develop urinary stones. Table 3 shows that a high proportion of those with chronic dehydration also had a dietary risk factor, namely intake of foods rich in oxalate or calcium or both. Thus 32/54 patients with a history of a hot climate showed a dietary risk factor, as did 35/61 patients with a single cause of dehydration.

The most common dietary risk factor was high oxalate intake in every category of dehydration examined.

It might be thought that the "pre-advice" 24-h urinary volume of 1720 ml was surprisingly high. However, it must be remembered that these patients were all secondary or tertiary referrals to the metabolic stone clinic and some had certainly been advised to drink extra water before being called to the clinic. The effect of this advice was followed by a substantial rise in the 24-h urinary volume of 755 ml. This was considerably higher than the

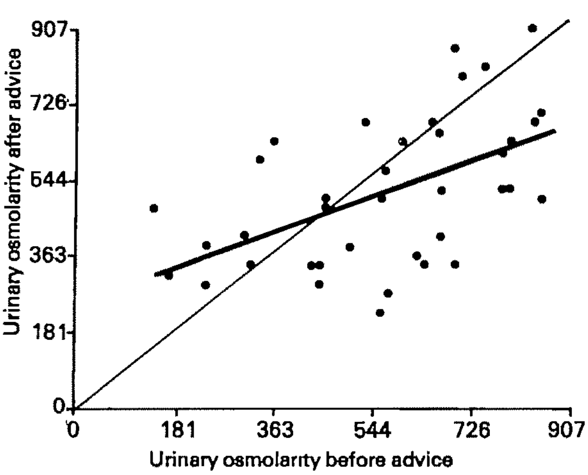

Fig. 2 Comparison of urinary osmalarities of random samples of urine before and after advice to increase water intake Thin line: line of equivalence. Thick line: regression line. Each point uses means for each patient.

increase of 267 ml/day found by Frank and de Vries (1966) and which resulted in a large reduction in the stone recurrence rate. One must also consider the effects on the calcium oxalate content of the urine following increased water intake. Table 4 shows that mean 24-h urinary calcium rose by 0.94 mmol, which was statistically significant. This rise was presumably because the water in London and surrounding areas is high in calcium content, with a concentration of about 2.7 mmol/l. Therefore an increase of 755 ml of water intake would be accompanied by 2.0 mmol of calcium and absorption of 50% of this would not be surprising. However, one could calculate from Table 4 that the mean urinary calcium concentration fell from 3.5 mmol/l before advice to 2.8 mmol/l after advice, which is a satisfactory outcome. Moreover, 24-h urinary oxalate showed no statistically significant rise after advice and the oxalate concentration fell from 0.156 to 0.118 mmol/l. The product of calcium × oxalate concentrations therefore fell from 0.546 before advice to 0.332 afterwards, a fall of 30%.

There appeared to be a significant reduction in the osmolality of random samples of urine in these patients with initially high values. Nevertheless, it was disappointing that the small fall in osmolality of the whole group was not statistically significant. Two reasons could have contributed to this. First, some of the pre-advice random samples were of remarkably low osmolality, perhaps due to advice already received elsewhere. Second, some of the patients travelled long distances to the clinic and found it inconvenient to drink on that particular day. The study of calcium oxalate crystals in these random samples was equally disappointing. Although there was a trend towards less crystals being present in the post-advice samples, this did not achieve statistical significance.

The long-term follow-up showed recurrences in only 7/98 patients. This is a low recurrence rate for a mean follow-up period of nearly 5 years. Others have found considerably higher rates of about 20% in 5 years (Ljunghall *et al.*, 1987) and 40% in 5 years (Rose, 1982). Moreover, several of these 7 patients had failed to attend the clinic until stone recurrence had occurred and urinary infection seemed responsible in 1 case. The recurrence rate in those who attended regularly and did not have urinary infection therefore seems to be encouragingly low and supports the idea that low urinary volume is the most important risk factor for urinary stone formation. The fact that a high oxalate intake occurred so frequently, also supports the view that this is the second most important risk factor for urinary stones. It is worth recalling in this connection that no less than 75% of the stones analysed were pure calcium oxalate and only 5.4% contained no calcium oxalate.

The finding that a high water intake is effective in preventing stone recurrence is not surprising and is in agreement with the results of Frank and De Vries (1966), Blacklock (1969), Milvy *et al.* (1981) and Rose (1982). The finding by Ljunghall *et al.* (1988) that a high urinary volume did not reduce the stone recurrence rate therefore requires consideration. In their patients the rise in mean urinary volume was very small: it rose scarcely at all in the first 5 years of follow-up, and in the next and final 3 years it rose by a mean of only 300 ml/day. Furthermore, it is not clear whether or not patients with raised urinary calcium were excluded from this study, as was done in the present study.

It might be argued that in hot climates low urinary volume is not the sole risk factor for stones that is increased. Thus urinary calcium may be raised (Parry and Lister, 1975) either because of increased drinking of hard water (as shown here) or because of increased exposure to sunlight and generation of vitamin D metabolites (Varghese *et al.*, 1989). The finding that chronic dehydration due to occupation or avoidance of water drinking also appears to cause urolithiasis is therefore of interest.

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The Authors

O. M Embon, MD, Deputy Head, Department of Urology, Rebecca Staff Government Hospital, Safed, Israel.

G. A. Rose, MA, DM, FRCP, FRCPath, Consultant Chemical Pathologist, St Peter's Hospitals

T. P. Rosenbaum, FRCSE, Lecturer, Institute of Urology.

Requests for reprints to: G. A Rose, Department of Pathology, St Paul's Hospital, 24 Endell Street, London WC2H 9AE.

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The Use of Internalised Ureteric Stents in Renal Transplant Recipients

J. V. THOMALLA, S. B. LEAPMAN and R. S. FILO

Departments of Surgery and Urology, Indiana University Medical Center, Indianapolis, USA

Summary—Since 1982, we have used internal indwelling ureteric stents for the management and prevention of ureteric reconstruction complications in 28 renal allograft recipients.

A total of 30 stents were placed in 18 patients either diagnostically or therapeutically in the management of allograft ureteric obstruction. In 16 patients internal stents were placed at the time of reconstruction for primary ureteropyelostomy (3), secondary ureteropyelostomy (8), repeat reimplant (3) and repair of ureteric or pelviureteric junction injury (2).

Complications included 3 episodes of transplant pyelonephritis, proximal stent migration (1), persistent bacteriuria (1) and prolonged healing of a ureteropyelostomy (1).

Internalised ureteric stenting is a safe and effective means of managing or preventing ureteric reconstruction complications in renal transplant recipients.

The majority of urological complications that befall the renal transplant population occur early (<3 months after transplantation) and are secondary to poor healing of the cystotomy or reimplant site, resulting in fistula formation. As a result of the poor healing demonstrated by patients receiving steroid immunosuppression, it has become customary to explore these patients to limit the potential for further morbidity and mortality (Thomalla *et al.*, 1985).

The incidence of late urological complications is less frequent. These complications usually follow ischaemic changes induced in the ureter because of poor harvesting technique which compromises the ureteric blood supply, or gradual ischaemia resulting from chronic rejection of the ureteric vasculature's endothelium. Both of these events result in ureteric fibrosis, stricture, aperistalsis and subsequent obstruction. When late complications arise, these patients are so often stabilised on lower doses of immunosuppression and conservative management is often chosen initially, with internalised ureteric stenting. This permits definition of the anatomy and assesses the potential for recovery of renal function. Stenting alone may also be therapeutic in selected cases.

Internal ureteric stents have been used previously in the management of ureteric complications in renal allograft recipients (Berger *et al.*, 1980), but their role has not been well defined.

We report our experience with internal ureteric stents placed in 28 renal allograft recipients for the management and prevention of ureteric reconstruction complications.

Patients and Methods

We have used the patient's native or reconstructed urinary bladder in 899 of 902 renal transplants performed at this centre between July 1974 and October 1988. In the 3 exceptions loop diversions were used (2 ileal and 1 colon).

Our standard ureteric reconstruction is a modification of the Leadbetter-Politano ureteroneocystostomy. Working through an anterior cystotomy, the donor ureter is brought through a laterally placed bladder wall hiatus and then channelled submucosally into the posterior aspect of the trigone. The ureteric anastomosis is anchored to the trigone at its distal apex with a 4/0 suture and completed with interrupted 5/0 sutures between the mucosa of the bladder and ureter. The mucosa over the hiatal defect is closed with a running 5/0 suture.

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The bladder is closed in 2 layers—a running inner mucosal muscular layer and a second layer of interrupted seromuscular sutures in an inverting Limbert fashion using 3/0 sutures. Chromic or Polydioxanone is used depending on the surgeon's preference. The bladder is left to gravity drainage for 4 days. On the fifth post-transplant day the catheter is removed and the patient is instructed to void frequently, gradually increasing the interval and volume between voidings.

The wound is observed daily for evidence of fluid accumulation or drainage. If fluid is present, a sample is collected and the creatinine and urea nitrogen determined and compared with current serum values. With normal renal function, urine values should be significantly higher. Should any question arise concerning the integrity of the urological reconstruction, a cystogram (and, if necessary, an intravenous urogram) is obtained. If contrast extravasation is identified, the patient undergoes exploration.

Patients are followed up periodically on an outpatient basis with serial laboratory determinations including serum blood urea nitrogen (BUN), creatinine and 24-h creatinine clearance. If declining renal function is discovered, the patient undergoes a nuclear renal scan (DPTA) and ultrasound of the allograft.

When obstruction is identified, the patient undergoes retrograde pyelography to assess the site and degree of obstruction as well as the potential for stenting. Stenting procedures are performed under general anaesthesia. Under fluoroscopic visualisation a guide wire (0.038 inch) is passed into the collecting system over which a double J stent is introduced. We have used 5 or 6 F stents in lengths of 10 to 12 cm. The native ureters are examined at the same time to evaluate their suitability for reconstruction should that become necessary.

When stents are placed during open procedures, the guide wire is employed either retrograde for reimplantation or antegrade for a ureteropyelostomy. Should ureteropyelostomy be performed, the bladder should be full at the time of passing the guide wire and stent to ensure that the bladder has been entered (fluid will reflux up through the stent when the stent is in the lumen of the bladder). A KUB is obtained post-operatively to verify the position of the stent. All patients receive perioperative cephalosporin antibiotic prophylaxis and are maintained on oral cephalosporin or trimethoprim/sulphamethoxazole while the stent is in place. If the stent is to remain indefinitely, it is changed every 4 to 6 months to prevent encrustation or blockage by debris.

Results

Since 1982, we have used internalised ureteric stents for the management and prevention of ureteric complications in 28 renal allograft recipients. A total of 46 stents have been placed. Two categories were established: (1) diagnostic/therapeutic and (2) reconstruction. There has been some overlap of patients between these 2 groups during their course of therapy.

In category 1, 18 patients have undergone 30 stent placements. Since 1982, an attempt to place a retrograde stent was made at the time of diagnosis of ureteric obstruction. A total of 4 patients were unable to be stented retrogradely and percutaneous nephrostomy was required with subsequent placement of an antegrade stent in 2 cases. The other 2 patients were also unable to have an antegrade stent and underwent immediate open reconstruction. There were 13 cadaveric recipients and 5 living related. These patients presented with declining renal function and obstruction 3–149 months after transplantation (mean 49 months). The cause of ureteric obstruction was presumed to be secondary to ischaemic changes with resultant fibrosis and areas of aperistalsis in the majority of patients (15/18). The other causes were infection (2) and a lymphocele (1).

Review of the retrograde pyelogram and the patient's overall clinical status dictated the choice of treatment. In patients where obstruction was presumed to be secondary to a short stricture, conservative management with an indwelling stent was chosen in anticipation of dilating the fibrosed segment (Fig. 1). Of 5 patients managed in this way, the obstruction was resolved in 3 after an average stented period of 3.7 months (range 1–6) and they have remained free of obstruction for 2 to 4 years. The other 2 patients required reconstructive procedures after conservative management of similar duration had failed. All 5 patients have functional grafts.

Conservative management was adopted in 8 other patients whose clinical status or degree of renal dysfunction was felt to contraindicate aggressive surgical management; 6 of these patients lost their graft as a result of chronic rejection, 1 died of disseminated herpes and the other has a functional graft undergoing periodic stent change (Fig. 2).

Of the 5 remaining patients in this category, 4

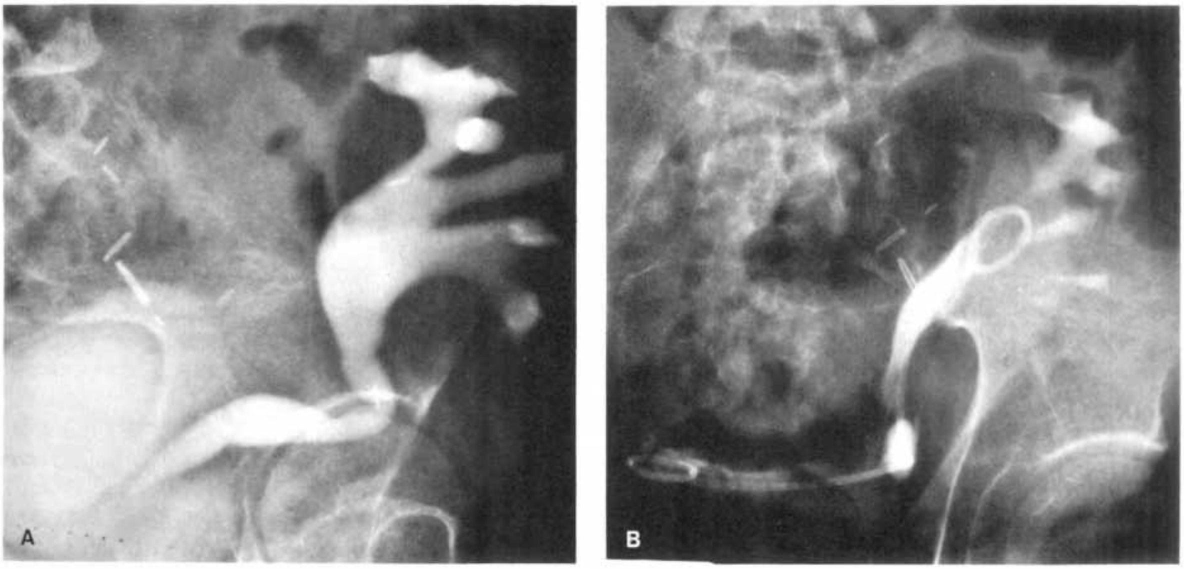

Fig. 1 (A) Patient D.C. presented 3 months after a living related renal transplant with declining renal function. This IVU at 30 min demonstrates moderate hydronephrosis with a distal ureteric stricture. (B) Following placement of an internal stent, the IVU was repeated. This 5-min film shows resolution of the hydronephrosis. The stent was subsequently removed with no recurrence of hydronephrosis. It is now 3 years since distal ureteric dilatation.

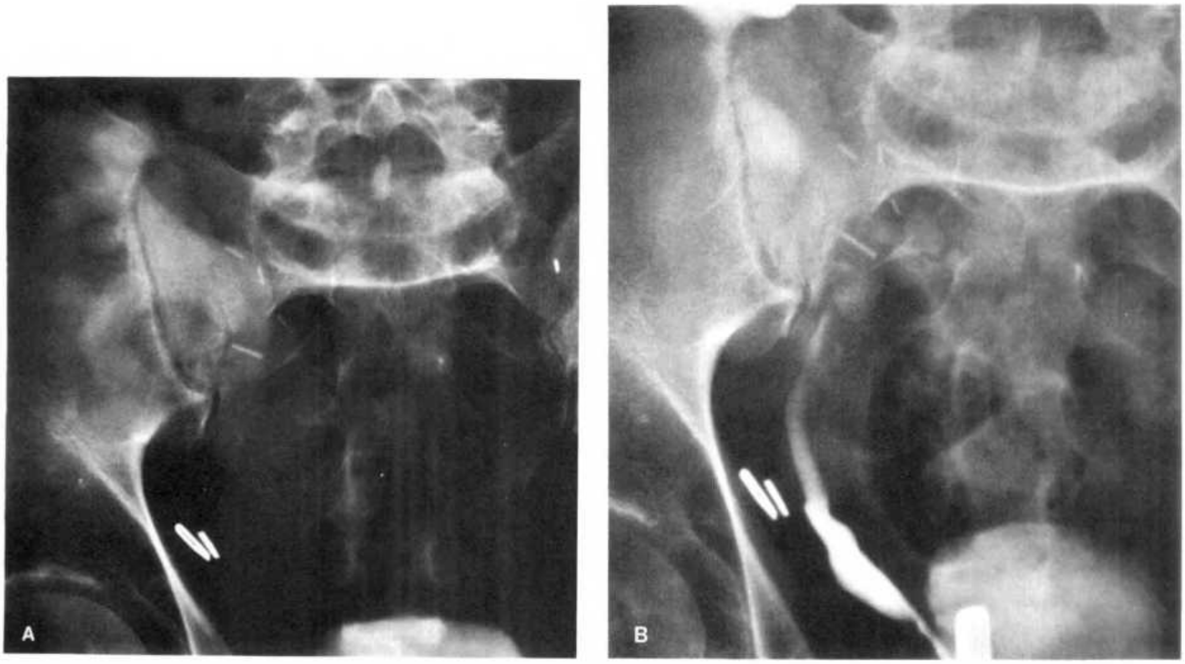

Fig. 2 (A) Patient E.Y. presented 69 months following a cadaveric renal transplant with elevated BUN and creatinine. An IVU demonstrated significant hydronephrosis with columnation at the vesicoureteric junction at 1 h. (B) Retrograde pyelogram demonstrates a distal ureteric stricture. The ureter was stented for a prolonged time as the patient required a coronary artery bypass. An attempt to remove the stent was followed by a rapid decline in renal function. The stent was replaced and has been changed every 6 months since then.

underwent early reconstruction and the other underwent lymphocele drainage (with subsequent resolution of ureteric obstruction). All 5 have functional grafts.

There were 16 patients in Category 2 (10 cadaveric, 6 living related) who underwent reconstructive procedures using indwelling ureteric stents 1 day to 139 months after transplantation (average 30.3 months). Three primary placements were performed at initial reconstruction employing ureteropyelostomy (2 donors with pelviureteric junction obstruction, 1 with transected ureter at harvest). The other 13 patients underwent a secondary reconstructive procedure for obstruction (8), ureteric injury (3) and fistula formation (2) (ureteropyelostomy in 8, repeat implant in 3 and repair of the injury in the other 2). Of these 16 patients, 12 have functional grafts and 4 have lost their grafts secondary to chronic rejection.

Complications of stent placement have been rare: transplant pyelonephritis (3), proximal stent migration (1) and persistent bacteriuria (1). In addition, a primary ureteropyelostomy was re-explored because of urinary extravasation which was found to be the result of the stent placing tension on the anastomosis, resulting in non-union of the mucosal edges (Fig. 3).

Discussion

In our experience of 902 renal transplants performed between July 1974 and October 1988, we have encountered urological complications requiring open repair in 49 recipients; a further 11 recipients developed complications that required stenting alone (urological complication rate 6.7%). Of these complications, 37 (62%) developed early (<3 months) following transplantation. Of these early complications, 22 (59%) were bladder leaks, 9 (25%) were ureteric fistulas and 6 (16%) were ureteric obstructions.

Late complications involved the ureter in 22 of 23 patients; 21 of these were obstructive in nature and the remaining late ureteric complication was a

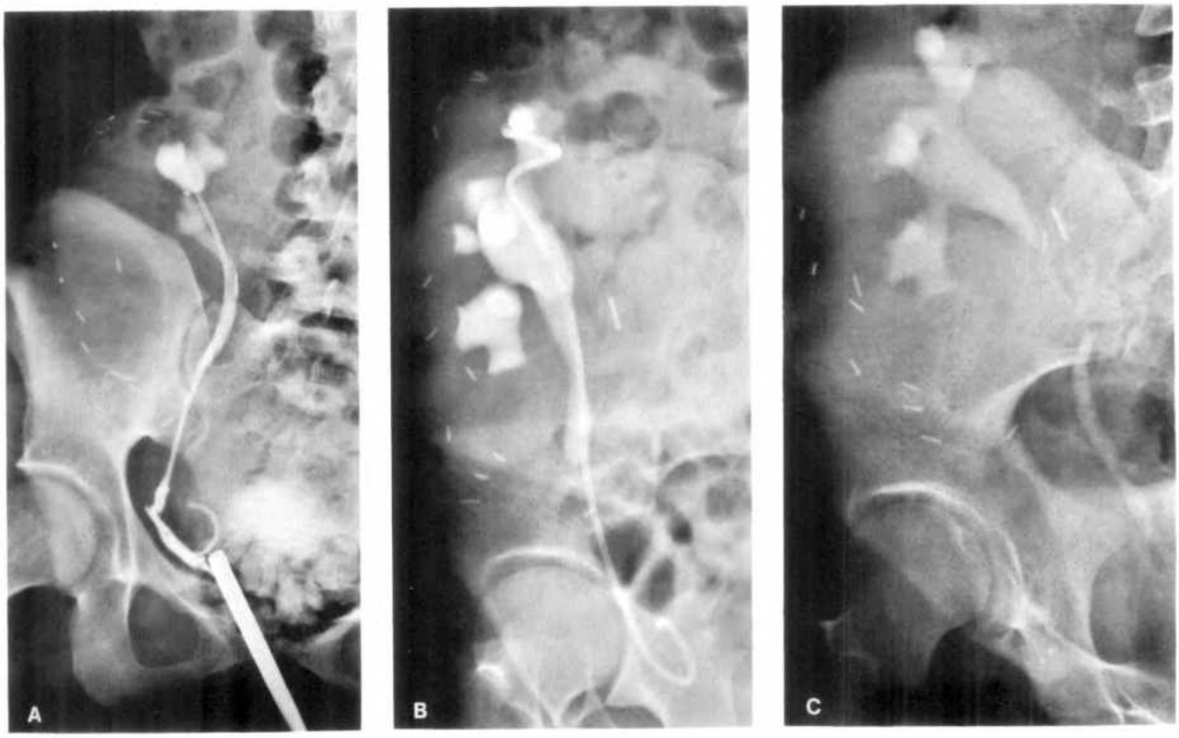

Fig. 3 (A) Patient T.N. presented 4 months after a cadaveric renal transplant with the diagnosis of transplant pyelonephritis. Ultrasound demonstrated hydronephrosis and resulted in this retrograde examination which was done around the ureteric stent to visualize the stricture better. The ureter appears to be strictured from the mid-portion to the vesicoureteric junction. (B) This intravenous urogram was made after the patient's renal function returned to baseline and demonstrates complete cut-off at the mid-ureter. (C) Because of the length of the stricture it was decided to perform a host-to-graft ureteropyelostomy. This post-reconstruction IVU shows prompt function at 5 min with complete filling of the native ureter.

fistula caused by a renal biopsy. The only late bladder complication was in a patient who developed a neurogenic bladder 3 years after transplantation, requiring bladder augmentation. This summary of urological complications is comparable with those of other recent reviews (Waltzer *et al.*, 1980; Sagalowsky *et al.*, 1983).

Most urological complications occur early and are secondary to fistula formation from either the cystotomy or the reimplant site. Wound and perineal/genital swelling (with or without drainage) is the most common presentation of these complications.The leak is easily identified with cystography and confirmed by measuring the BUN and creatinine of the wound drainage.

It has been our policy to repair these early fistulas with an open surgical procedure. We have done this in an attempt to prevent the potential morbidity and mortality that might otherwise be associated with non-operative management (*i.e.* chronic drainage systems leading to urinary tract infection, wound infection and sepsis). Open repair provides for a direct, sutured anatomical approximation which reduces the potential for non-healing. Prevention of a chronic urinary fistula also reduces the potential for chronic infection, sepsis and wound breakdown. Although stenting and bladder drainage have been used by others as conservative management for early fistulas, the frequent failure of this approach, coupled with the prolonged time that might be required for resolution of the fistula, has led us to believe that there is only a very limited use for ureteric stenting as primary treatment for an early ureteric or bladder fistula (*i.e.* an unstable patient) (Desai *et al.*, 1971; Morehouse *et al.*, 1973; Schiff *et al.*, 1976; Sagalowsky *et al.*, 1983).

The presentation of late complications is almost always secondary to an obstructed ureter. These patients have usually enjoyed stable renal function and are discovered during follow-up to have an abrupt decline in function which results in urological evaluation. The location, degree and length of the obstructed ureter must be delineated in order to determine the therapeutic approach. This is most readily done with retrograde pyelography. Once the anatomy is demonstrated, the ureter can then be stented. Should the retrograde approach not be feasible, a percutaneous nephrostomy will be required.

With the stent in place, many factors must be considered before selecting any form of therapy. The first factor to be evaluated is recovery of renal function. Patients with recoverable renal function generally achieve this within 48 h of relieving the obstruction, although in a number of patients this has taken a month or more. Should renal recovery by delayed beyond this time, there is little chance of reversal if the dysfunction is secondary to obstruction alone. We usually perform a renal biopsy on these patients to rule out the possibility of occult rejection and confirm the presence of irreversible fibrosis. When obstructive injury has resulted in significant loss of renal function we are less inclined to perform a major reconstructive procedure, electing rather to manage the patient with periodic stent changes.

Of importance also is the patient's ability to tolerate a major reconstructive procedure. Such procedures are generally straightforward and we have observed very little morbidity and no mortality in our patients. However, should the patient have other major disease processes that are active, the risk to benefit ratio must be assessed, particularly if there has been marginal recovery of renal function.

The anatomy of the stricture must also be considered. A short stricture of the distal ureter may be amenable to dilatation with passage of a stent. In our attempt at conservative management of short ureteric strictures with stenting alone, we were successful in 3 of 5 patients, the other 2 requiring open procedures.

A pan-fibrotic ureter, however, may not be successfully treated in this way because of the loss of peristaltic activity, with the ureter becoming a fixed obstructive conduit. It has been our policy to proceed to a bypass procedure, most commonly a host-to-graft ureteropyelostomy if adequate native ureter is present (Fig. 3). Streem *et al.* (1988) reported their experience using balloon dilatation of ureteric strictures with good results in 5 of 11 patients. The reason for failure was recurrence of obstruction; however, delineation between a point stricture or pan-ureteric fibrosis was not made. It may be that these balloon failures were in patients with pan-ureteric fibrosis where aperistalsis remained following dilatation, thus contributing to obstruction. Unlike Streem *et al.* (1988), we have reserved the percutaneous approach after failure of a retrograde attempt. We have been successful in retrograde cannulation in 14 of 18 attempts (78%) and therefore have refrained from using a primary percutaneous approach due to the potential risks involved with placement of a nephrostomy in these patients with a solitary kidney (bleeding, arteriovenous fistula formation, infection secondary to percutaneous contamination of the renal pelvis). We have found that in 2 of 4 patients in whom a retrograde stent could not be placed, it was also impossible to place an antegrade stent. This resulted from the angularity of the ureter caused by fibrosis. The antegrade approach has the disadvantage of trying to pass the wire through what is often the densest portion of the obstructed ureter (the vesicoureteric junction) at the greatest distance from the operator where the least amount of torque and force can be exerted. However, with retrograde placement the vesicoureteric junction can be directly manipulated and once the guide wire can be navigated through the vesicoureteric junction, it usually passes with ease into the renal pelvis. Considering the ease with which percutaneous nephrostomy can be performed under ultrasound guidance and local anaesthesia, these concerns may become minimal in the future.

We have chosen to use internal stents in all primary ureteropyelostomies and all secondary ureteric reconstructions. We believe that stenting provides a means by which to drain urine away from the repair without allowing the anastomosis to become "dry", thus reducing the incidence of subsequent fibrosis. A stent also provides a template over which the repair can heal; this is particularly important in the steroid recipient (Thomalla *et al.*, 1985). Finally, the integrity of the repair can be easily assessed by cystography, where contrast can freely reflux up through and around the stent, demonstrating any extravasation that may be present. When using stents in conjunction with a reconstructive procedure, the stent must be placed so that it will not bow out against the anastomosis (particularly with ureteropyelostomy), thus promoting non-union and subsequent fistula formation.

The morbidity rate of both long- and short-term stenting has been acceptable and has been limited primarily to the infectious complication of transplant pyelonephritis (Thomalla *et al.*, 1989). We continue to maintain these patients on prophylactic antibiotics while the stent is in place.

Internal ureteric stenting is a useful adjunct in the management and prevention of ureteric reconstruction complications in renal allograft recipients. It appears to be most useful in later obstructive complications by providing a means by which to bypass the obstruction and assess the potential for recovery of renal function.

In selected cases (patients with short strictures), ureteric stenting may be therapeutic as it dilates the point of obstruction. In other patients where reconstruction is contraindicated, chronic stenting may be therapeutic indefinitely or until the graft fails. Internal ureteric stenting also appears to be an effective adjunct for ureteric reconstruction in renal allograft recipients in selected primary and all secondary procedures.

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The Authors

J. V. Thomalla, MD, Staff Urologist, Marshfield Clinic.

S. B. Leapman, MD, Professor of Surgery, Indiana University Medical Center

R S. Filo, MD, Professor of Surgery, Indiana University Medical Center.

Requests for reprints to. J. V. Thomalla, Department of Urology, Marshfield Clinic, Marshfield, WI 54449, USA.

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Ureteric Substitution with Boari Bladder Flap

H. G. MOTIWALA, S. A. SHAH and S. M. PATEL

Department of Urology and Transplantation, Institute of Kidney Diseases and Research Centre, B.J. Medical College, Ahmedabad, India

Summary—Between 1986 and 1989, 12 patients underwent ureteric substitution with a Boari bladder flap at this Institute. The indications were ureteric injury following hysterectomy, difficult forceps delivery, difficult ureterolithotomy, ureteric strictures caused by a Dormia basket and previous ureteric surgery, tuberculosis, retroperitoneal fibrosis and a post-ureteric reimplantation fistula.

There were 2 patients with a solitary kidney and 2 in acute renal failure. Double J stenting was carried out in 11 patients and the stent was removed 3 to 6 weeks post-operatively. Good results, with no morbidity or mortality, were achieved in all but 1 patient where a simple Silastic stent had migrated to the pelvis and required open surgery to remove it. We attribute our success to the tension-free anastomosis, a wide based posterior flap with preservation of its vascular supply, the use of a double J stent and vicryl suture material.

The Boari bladder flap is an excellent reconstructive urological procedure to bridge the gap caused by loss of the lower ureter, and thereby preserving renal function. Transuretero-ureterostomy and the psoas hitch (Turner-Warwick and Worth, 1969) are alternative procedures. Thompson and Ross (1974) and Bowsher *et al.* (1982) prefer the Boari flap to other methods.

Patients and Methods

From 1986 to 1989, 12 patients underwent ureteric substitution with a unilateral Boari bladder flap. There were 7 females and 5 males and their ages ranged from 13 to 57 years (mean 34). Two patients had a solitary kidney and 2 were in acute renal failure. The indications for the procedure are depicted in the Table. Most of the patients were referred following ureteric injury.

An example of a typical patient was a woman who had had a difficult hysterectomy and a solitary left kidney where the ureter was ligated in the pelvis. She presented with severe hydroureteronephrosis on the left side and acute renal failure. An emergency percutaneous nephrostomy was performed. The nephrostomy stent broke later and migrated down the ureter to the site where the ureter was ligated (Fig. 1). The patient developed a stricture which was corrected successfully with a Boari bladder flap and removal of the foreign body.

We used an extraperitoneal approach with an extended lateral iliac incision in all patients. The pelvic ureter was replaced with a bladder tube up to the sacral promontory. The bladder was mobilised on the lateral, medial and posterior aspects; the flap had a trapezoid shape, with a base of 4 cm (minimum) and apex of 3 cm and was based on the posterior wall. End-to-end anastomosis between the ureter and flap was performed in 7 patients

Table Indications

Indications	*No. of patients*
Post-hysterectomy ureteric injury	3
Retroperitoneal fibrosis	1
Ureteric injury during ureterolithotomy	1
Post-Dormia ureteric stricture	2
Injury to lower ureter during difficult forceps delivery	1
Post-ureterolithotomy stricture	2
Post-ureteric reimplantation fistula	1
Tuberculosis	1

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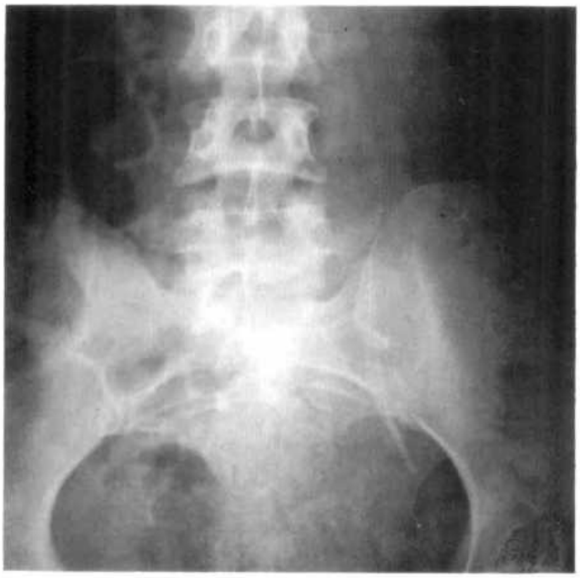

Fig. 1 Case no. 6. Migrating nephrostomy stent on left side.

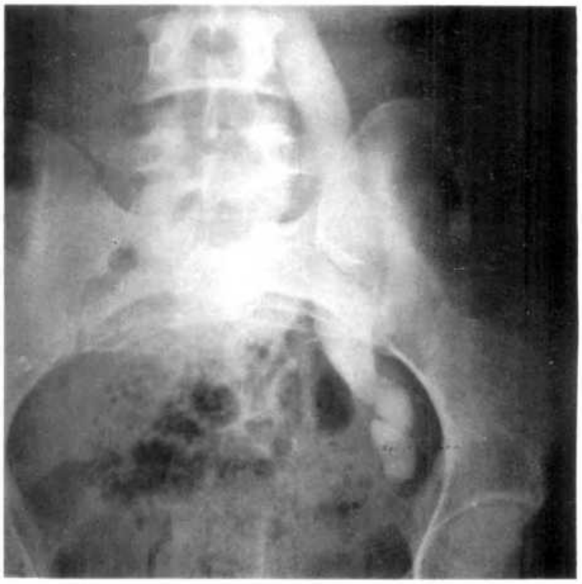

Fig. 2 Case no 5. Ligation of left ureter during hysterectomy.

where the ureter was dilated and of adequate length. Submucosal tunnelling with an anti-reflux anastomosis where the ureter was minimally dilated was carried out in 5 patients. A double J stent was used in all except the first patient, where an infant feeding tube was used as a stent. Anastomosis was carried out with 4/0 vicryl and 3/0 vicryl was used to form the vesical tube, with continuous inner and interrupted outer sutures. The post-operative period was uneventful in all patients and a Foley catheter was left indwelling for 5 to 7 days. The drain was removed 24 h after removal of the catheter. The double J stent was removed between 3 and 6 weeks post-operatively and an IVU was performed in most cases 3 months post-operatively.

Results

Of the 12 patients with a Boari flap, 7 had suffered ureteric injury. Post-hysterectomy ureteric injury was noted in 3 patients (Fig. 2) and Dormia-related strictures in 2; all flaps were unilateral. Good results were achieved in all cases and there was no mortality or morbidity (Fig. 3). One patient had migration of a stent in the pelvis of a kidney and open surgery was required to remove it. Post-operative urine cultures were positive in 8 patients after 1 week and the urine showed pus cells while the stent was *in situ*. All patients had sterile urine after removal of their stents.

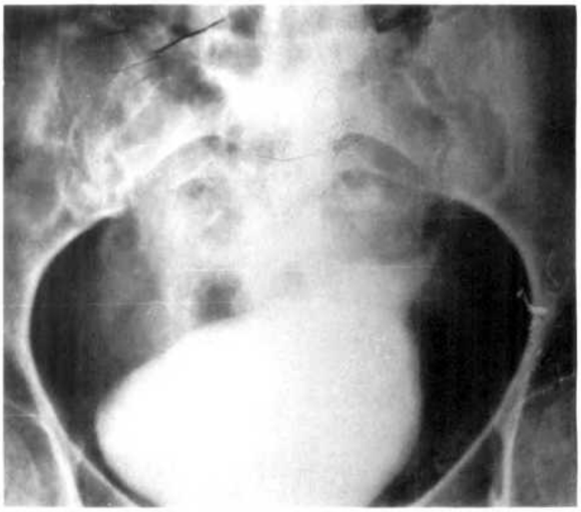

Fig. 3 Post-operative voiding cystourethrogram after Boari flap procedure; no reflux detected.

Discussion

Van Hook proposed the use of a bladder flap in 1893 (Turner-Warwick and Worth, 1969) but the first description came from Boari in 1904 in relation to dogs. It was not until 1930 that Baidin used the flap in man (Gow, 1968). Ockerbald has since popularised the technique in the United States (Koontz *et al.*, 1986).

In our experience, the use of a Boari bladder flap to replace the pelvic ureter led to excellent results in terms of ureteric substitution with preservation of renal function. With the popularisation of the psoas hitch by Turner-Warwick and Worth (1969) and the emergence of transuretero-uterostomy, the indications for a Boari flap decreased (Zingg, 1984), although good long-term results have been reported by others (Pearson, 1970; Thompson and Ross, 1974; Kuss and Chatelian, 1984). There are situations where full mobilisation of the bladder may be impossible because previous surgery makes a psoas hitch difficult, and transuretero-uterostomy has a higher complication rate (Ehrlich and Skinner, 1975; Boxer *et al.*, 1984). Transutero-uterostomy requires a good contralateral functioning kidney. Although a bilateral Boari flap may be used in selected patients, it is technically difficult.

We feel that the use of a Dormia basket has increased the incidence of ureteric strictures (2 cases in the present series) and this has also been reported by Bowsher *et al.* (1982).

Candidates for the Boari bladder flap must have a normal bladder capacity with no fibrosis of the bladder wall, since success depends on having a long vascularised flap with tension-free anastomosis. We routinely use an extraperitoneal approach, and stay sutures for marking the flap were inserted when the bladder was half filled.

What type of anastomosis should be used—direct end-to-end or anti-reflux with submucosal tunnelling? In essence, the tubularised flap is an artificially created diverticulum of the bladder and has no functional activity as a tube; therefore the opening must always be wide mouthed in order to drain well (Koontz *et al.*, 1986). Kuss and Chatelian (1984) recommended direct anastomosis but Zingg (1984) stressed that reflux is bound to occur in direct anastomosis and that the long-term effects of reflux might be damaging and potential drawbacks of the submucosal tunnel like diminished ureteric length at operation, increased incidence of pre-anastomotic stenosis and difficulty in retrograde ureteric catheterization are insignificant. We prefer a submucosal tunnel with an anti-reflux anastomosis when the ureter is minimally dilated and of adequate length, but when the ureter is extremely dilated we use an end-to-end anastomosis. It is essential that the anastomosis is free from tension.

We routinely stent the ureter with a double J stent. The cost factor has forced us to re-use the stents after sterilisation for 48 h in a formalin chamber.

Use of a double J stent has reduced the incidence of urine leakage and infection. Good long-term results have been confirmed by post-operative IVU, where the vesical tube is hard to identify. We attribute our success to the wide-based bladder flap with tension-free anastomosis and the use of a double J stent together with vicryl sutures.

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The Authors

H. G. Motiwala, MB, MS, Fellow in Urology and Transplantation.

S. A. Shah, MB, MS, MCh, Assistant Professor in Urology

S M. Patel, FRCSE, Honorary Professor and Head of Department of Urology.

Requests for reprints to: H. G Motiwala, c/o Mr Z Iqbal, "AMAN", Opp. Parasbaug Society, Behind Tagore Hall, Ellisbridge, Ahmedabad 380 006, India.

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Effect of Bladder Outflow Obstruction on the Innervation of the Rabbit Urinary Bladder

S. C. W. HARRISON, D. R. FERGUSON and P. T. DOYLE

Department of Urology, Addenbrooke's Hospital; Department of Pharmacology, University of Cambridge, Cambridge

Summary—The effects of bladder outflow obstruction on the innervation of the bladder were studied using a rabbit animal model. Partial occlusion of the bladder neck was obtained by the placement of a silk ligature at that level; control animals underwent a sham procedure. After a 3-month period, the presence of outflow tract obstruction was confirmed using urodynamic studies. The animals were then killed and pharmacological assessments of the bladder innervation undertaken.

Detrusor muscle strip studies provided evidence of damage to the cholinergic innervation of the detrusor. Also, muscle strips from obstructed animals showed reduced inhibitory responses to β-adrenergic stimulation with isoprenaline. In addition to these muscle strip studies, the bladder content of the neuropeptide substance P was assayed, but no significant change was observed in response to obstruction. This finding suggests that substance P-containing sensory nerves may be spared from the denervating effect of bladder outflow obstruction.

Bladder outflow obstruction has been shown to lead to a loss of cholinergic post-ganglionic parasympathetic nerves from the bladder wall. This denervation of the detrusor muscle has been demonstrated in man and in the pig using both pharmacological and histological techniques (Sibley, 1984, 1987; Gosling *et al.*, 1986; Speakman *et al.*, 1987). A further pharmacological study using muscle strips from the bladders of patients undergoing endoscopic outflow tract surgery has suggested that detrusor denervation is associated with the presence of detrusor instability (Harrison *et al.*, 1987).

The present study examined the effect of outflow tract obstruction on the bladder's innervation in a further species. Information was sought to determine which categories of nerve are susceptible to the damaging effects of obstruction. Muscle strip studies were used to assess the cholinergic and non-cholinergic elements of the detrusor innervation. Responses to isoprenaline were examined since noradrenaline, released from sympathetic nerves, may exert an inhibitory influence on the detrusor by its action on β-receptors. Finally, measurement of the substance P content of the bladders was used to indicate whether there was evidence of damage to substance P-containing sensory nerves. Studies using the sensory neurotoxin capsaicin have indicated that a substantial proportion of the substance P content of the rabbit urinary bladder is present in sensory nerves (Harrison, 1988).

Materials and Methods

Male New Zealand White rabbits weighing between 2 and 2.5 kg were used. Urodynamic studies were performed prior to either a procedure partially to occlude the bladder neck (14 rabbits) or a sham control operation (6 rabbits). Three months postoperatively, repeat urodynamic studies were undertaken. The following day the rabbit was killed and the bladder removed so that muscle strip studies and substance P assays could be performed.

Urodynamic studies were carried out on sedated animals; pentobarbitone sodium was administered via an ear vein at a dose that was titrated to the

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point where the animal would lie supine and not attempt to right itself (a dose of 30 mg was usually appropriate). The rabbit bladder was catheterised with a 4 F infant feeding tube and the animal placed in a restraining box which served to keep it still during the study. The box allowed sufficient room for the changes in posture that accompany voiding and had a slatted floor so that the voided urine did not wet the rabbit; 5-ml volumes of normal saline at room temperature were instilled into the bladder at 1-min intervals; intravesical pressure was monitored using a pressure transducer with the amplified signal being recorded on a chart recorder. The parameters measured included the volume required to give a rise in intravesical pressure of 5 cm H_2O (a value reflecting early filling compliance), the volume and pressure thresholds for micturition, peak voiding pressure and the residual urine volume. The filling/voiding cycle was repeated 2 or 3 times and the results averaged.

A technique for inducing partial obstruction at the bladder neck was described by Arbuckle and Paquin (1963); a modification of this method was used for the present study. The rabbit was anaesthetised and the bladder exposed via a lower midline abdominal incision. The bladder was not catheterised in order to minimise the risk of urinary infection. The seminal vesicles were separated from the back of the bladder and a 3/0 silk ligature was passed around the bladder neck; it was tied so as not quite to indent the serosa of the bladder while urine was being expressed from the bladder (which opened the bladder neck out into a funnel shape). The silk tie was adjusted in this way so that obstruction would develop slowly as a result of growth of the animal and progressive fibrosis around the ligature. Control animals undergoing a sham procedure had an identical dissection carried out but the silk ligature was omitted.

Urodynamic studies were repeated 3 months post-operatively and the following day the rabbits were killed by rapid intravenous injection of pentobarbitone sodium. The bladder was removed and urine sent for culture. The bladder was immersed in cold, oxygenated Krebs' solution, cleaned of extravesical tissue and subdivided into base, body and fundus. The base was defined as that part inferior to the attachment of the vasa deferentia, the fundus was the upper 2/5 and the body the lower 3/5 of the remaining segment. The anterior half of the bladder body was used for muscle strip studies and the remaining segments were frozen rapidly in liquid nitrogen for subsequent substance P assay.

In vitro muscle strip experiments were carried out on detrusor strips approximately 8 mm in length and 2 mm in diameter. They were stored for a maximum of 20 h at 4°C in oxygenated Krebs' solution. The strips were suspended in a superfusion chamber (capacity 0.2 ml) (Brading and Sibley, 1983) and superfused with Krebs' solution at 35°C at a rate of 1 ml/min. A loading tension of 0.5 g was applied and the strips allowed to equilibrate for 75 min before a 10-s control dose of carbachol (10^{-4} M) was administered. Isometric contractions were detected using a Grass FT03 tension transducer, amplified and recorded on a chart recorder. Experiments were carried out on muscle strips from obstructed and control animals in similar sequences; each animal provided up to 8 strips. Acetylcholine log dose response curves were constructed by measuring the responses to doses of the drug (range 10^{-7} to 10^{-2} M) administed over 10-s periods. Nerve mediated responses were examined using electrical field stimulation to construct frequency response curves (5-s trains of 50 V square wave pulses with a 50-μs pulse width at stimulation frequencies in the range 2.5–50 Hz). Stimulation parameters were chosen to stimulate the intramural nerves present in the muscle strips rather than the detrusor muscle fibres themselves; this was confirmed by the finding that the contractions resulting from stimulation could be inhibited using tetrodotoxin (3×10^{-7} M). Frequency response curves were also constructed in the presence of atropine (10^{-6} M) to examine non-cholinergic responses. The inhibitory effect of β-adrenergic stimulation on detrusor contractions was examined by producing log dose response curves to isoprenaline. Increasing concentrations of isoprenaline were added to the superfusate in the dose range 10^{-8} to 10^{-5} M; a standard stimulus was applied at each dose level in the form of a 10-s application of carbachol at a dose that produced a contraction that was 75% of the maximum response to cholinergic stimulation. In addition, a standard nerve-mediated contraction was applied at each dose level by stimulation using the standard parameters at 40 Hz. Finally, the sensitivity of the detrusor muscle to direct electrical stimulation was examined. Voltage response curves were constructed in the presence of tetrodotoxin (3×10^{-7} M) using single 100-ms stimuli in the voltage range 10 to 140 V; the tetrodotoxin served to block depolarisation of the intramural nerves so that contractions were the result of depolarisation of the smooth muscle cells.

The measurement of the substance P content of the bladders was undertaken by radioimmunoassay

(Too, 1985; Harrison, 1988). Tissue extraction was carried out following the thawing of the frozen bladder sections using a method based on that described by Too (1985). The bladder segments were weighed and finely chopped before 2 ml of 0.1 M boiling acetic acid was added and the tissue incubated for 10 min in a boiling water bath. The samples were then homogenised and centrifuged, aliquots of the resulting supernatant were separated and freeze dried. The resulting extracts were stored at −20°C until assay. The specific antibody used for the assay was α 140, which is directed against the N terminal fragment of substance P (Lee *et al.*, 1980; Too, 1985). The antibody was used at a final concentration of 1 in 40,000. The tracer peptide was ^{125}I Bolton and Hunter substance P. Incubations of antibody, tracer and tissue extract were carried out at pH 7.5 for 48 h at 4°C. A standard curve was constructed using known concentrations of substance P. Separation of the antibody/peptide complex was achieved by precipitation with cold absolute alcohol and centrifugation. The radioactivity in the resulting pellet was measured using a γ counter.

Statistical analysis of the urodynamic data and substance P assay results were carried out using the *t* test. Analysis of the response curves obtained from the muscle strip experiments was initially by computer curve fitting using a Hill equation. The resulting computer estimates of the EC_{50} (the stimulus required to produce a contraction which is 50% of the maximal response) and maximal response for the 2 groups of rabbits were compared using the *t* test. The Hill equation did not prove to be a suitable model for analysing the frequency response experiments. Analysis of these data was undertaken using a linear transformation programme to compare the 2 curves (Harrison, 1988).

All drugs used were obtained from Sigma Chemicals except for ^{125}I Bolton and Hunter substance P, which was obtained from Amersham International.

Results

Of the 14 rabbits which underwent an obstructing procedure, 8 survived the 3-month study period. One rabbit died of pneumonia and the other 5 developed complications related to urinary retention. None of the rabbits completing the study developed urinary retention. One further rabbit was found not to be obstructed both on urodynamic grounds and judging from the appearances of the bladder and ligature post mortem. One control rabbit died of pneumonia during the study period. The results are derived from the 7 obstructed and 5 control animals that completed the study.

The results of the post-operative cystometrograms are shown in the Table. The results for each animal were averaged from up to 3 cystometrograms. Data from the 2 groups were compared using the *t* test. No evidence of unstable bladder contractions was seen in any of the urodynamic studies.

Urine cultures grew staphylococci in 5 of the 7 obstructed and 3 of the 5 control animals. These were assumed to be contaminants introduced during catheterisation for urodynamic investigations the day prior to urine collection.

The bladders from the rabbits with outflow tract obstruction were found to be significantly heavier than those from control animals when compared using the *t* test; mean weights (±SEM) were 8.79 (±1.95) g and 3.32 (±0.80) g respectively ($P<0.05$).

Cholinergic responses of the muscle strips were examined firstly by applying a near maximal dose of carbachol (10^{-4} M) to all of the strips that were used. Mean tension for the obstructed group (± SEM) was 2.06 (±0.18) g (n=39). Values for the control strips were 2.70 (±0.22) g (n=32). These values differed significantly when compared using the *t* test ($P<0.05$), showing that muscle from obstructed bladders demonstrated a reduced capacity to generate tension in response to cholinergic

Table Urodynamic Data

	Obstructed Mean (±SEM) (n=7)	*Control Mean (±SEM) (N=4)*	*P*
Volume at 5 cm H_2O pressure (ml)	74 0 (±13.7)	92.3 (±22.9)	n.s.
Volume threshold for micturition (ml)	107.5 (±19.6)	103.0 (±26 4)	n.s
Pressure threshold (cm H_2O)	32.7 (±4.7)	9.5 (±2.1)	p<0.01
Peak voiding pressure (cm H_2O)	42.1 (±5.1)	15.3 (±2.3)	<0.01
Residual urine (ml)	48.5 (±5.4)	17.0 (±10.0)	<0.05

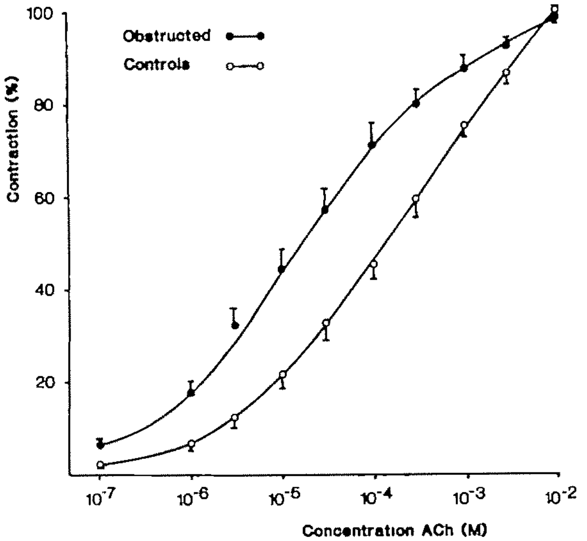

Fig. 1 Acetylcholine log dose response curves for muscle strips from obstructed (n = 20) and control (n = 16) rabbits. Contractions are expressed as a percentage of the maximum response obtained during the experiment. Values are means (±SEM) The computer generated best fit curves are shown, EC_{50} values for the 2 groups differed significantly

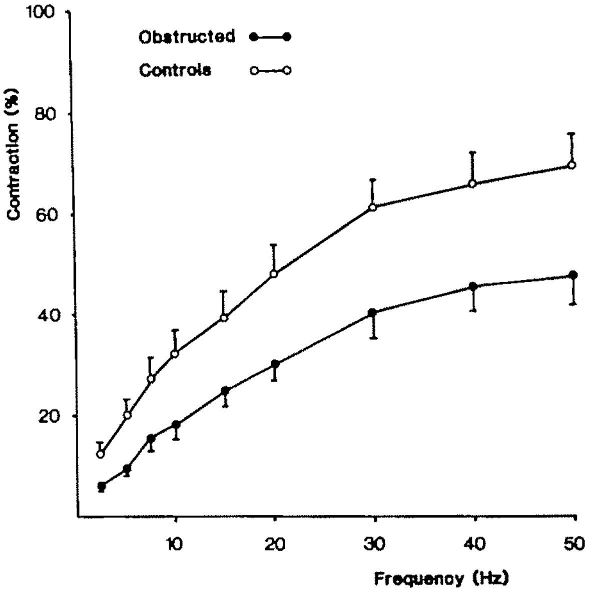

Fig. 2 Frequency response curves for muscle strips from obstructed (n = 18) and control (n = 16) rabbits. Contractions are expressed as a percentage of the maximum response obtained following exposure to acetylcholine Values are means (±SEM). The responses differed significantly.

stimulation. Acetylcholine log dose response curves for the 2 groups are shown in Figure 1. The curve for the obstructed group lies to the left of that for the controls; the computer estimated EC_{50} values (±SEM) were 1.61 (±0.10) $\times 10^{-5}$ M for the obstructed group and 15.4 (±2.27) $\times 10^{-5}$ M for the control group; this difference was significant ($P < 0.001$). This finding demonstrated that muscle from obstructed bladders was approximately 10 times more sensitive to acetylcholine than that from control bladders.

Nerve-mediated responses are presented in the form of frequency response curves. The data can be examined by expressing the contractions as a percentage of the maximal response of the muscle strip to cholinergic stimulation (Fig. 2) or as a percentage of the maximal response obtained during the construction of the frequency response curve (Fig. 3). The first method allows a comparison to be made between the maximum nerve-mediated responses while the second technique allows a clearer evaluation of any difference in sensitivity of the 2 groups of strips to field stimulation. Statistical analysis of the data was not possible using computer curve fitting since the Hill equation is not a satisfactory model of the frequency response relationship. The linear transformation technique demonstrated a significant difference between the 2 curves shown in Figure 3 ($P < 0.01$) but was not

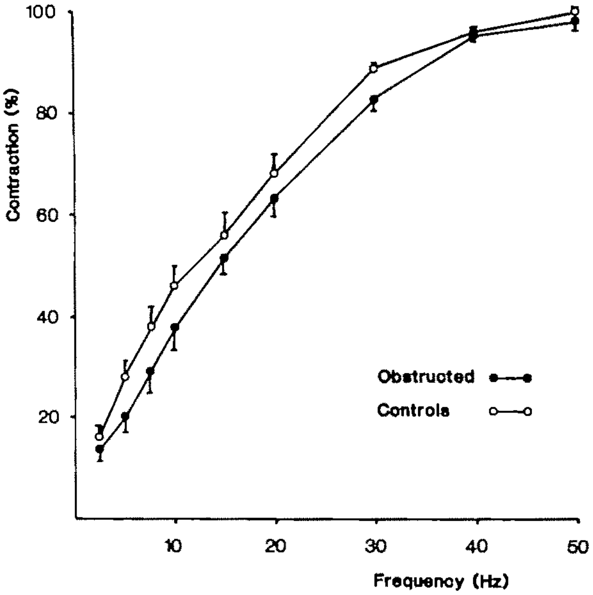

Fig. 3 Frequency response curves for muscle strips from obstructed (n = 18) and control (n = 16) rabbits. Contractions are expressed as a percentage of the maximum response obtained during the experiment. Values are means (±SEM). The curves were shown to differ significantly when analysed by the linear transformation technique.

applicable to the data from Figure 2 because an analysis of variance suggested that there was too much variability in the results to be sure that the transformation was valid. The responses shown in Figure 2 were compared using the *t* test and were found to differ significantly ($P<0.03$ at all frequencies). These results demonstrated that detrusor muscle from obstructed bladders showed both a reduction in sensitivity to nerve-mediated stimulation and a reduction in the maximum force of contraction that resulted from such stimulation.

The non-cholinergic (atropine-resistant) component of the nerve-mediated responses of the 2 groups is demonstrated in Figure 4. Statistical analysis by either curve-fitting or linear transformation proved not to be valid; use of the *t* test showed a significant difference for responses at 30 Hz ($p=0.03$).

The inhibitory effect of isoprenaline on the 2 groups of muscle strips was shown to differ significantly. Similar results were obtained whether contractions were obtained using field stimulation or carbachol. Figure 5 illustrates the isoprenaline dose response curves for the 2 groups using nerve-mediated contractions. Computer best fit estimates for the maximal degree of inhibition were 35.3 (±1.99)% for the obstructed strips and 59.8 (±0.74)% for controls ($P<0.001$). Detrusor muscle from obstructed bladders was therefore less responsive to β-adrenergic inhibition.

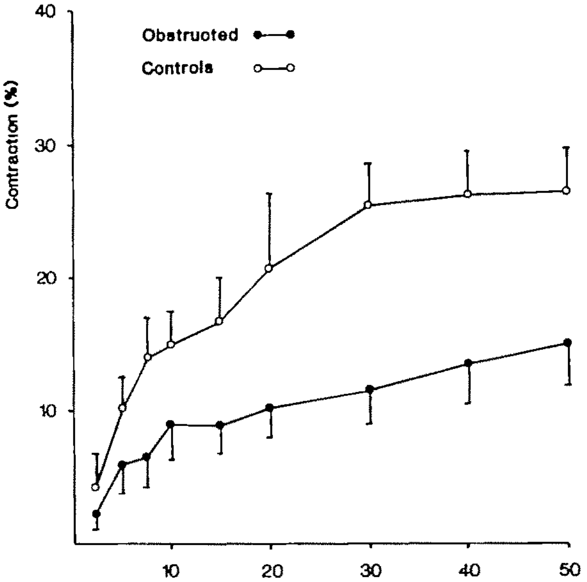

Fig. 4 Frequency response curves for muscle strips from obstructed (n = 7) and control (n = 8) rabbits constructed in the presence of atropine (10^{-6} M). Contractions are expressed as a percentage of the maximum response obtained in the absence of atropine. Values are means (±SEM). The responses at 30 Hz were shown to differ significantly

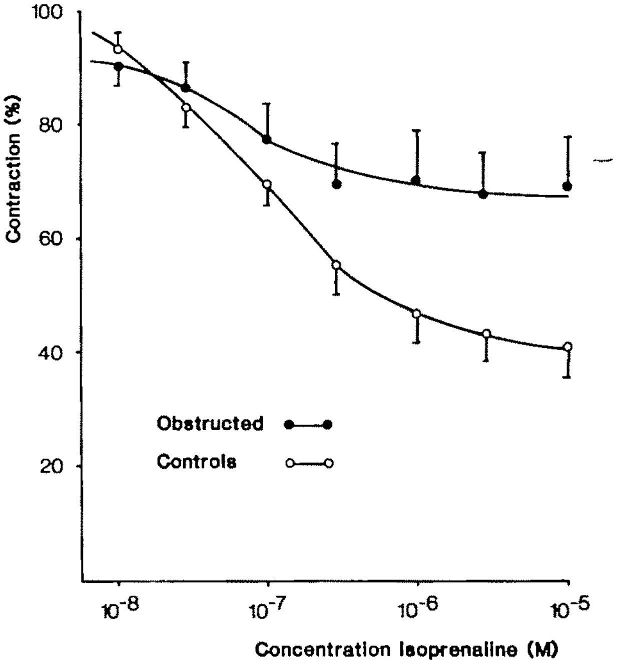

Fig. 5 Isoprenaline log dose response curves for muscle strips from obstructed (n = 11) and control (n = 8) rabbits. Contractions were elicited in response to electrical stimulation of the intramural nerves and are expressed as a percentage of the response obtained in the absence of isoprenaline. Values are means (±SEM). The computer generated best fit curves are shown; the levels of maximum inhibition differed significantly.

Voltage response curves are shown in Figure 6. The computer generated best fit curve for the obstructed group lies to the left of that for controls, suggesting that obstruction may lead to an increased sensitivity of the detrusor to direct electrical stimulation of its smooth muscle cells. However, the estimated EC_{50} values were 64.5 (±3.7) V for obstructed strips and 73.2 (±2.4) V for controls; this difference just failed to reach significance ($P=0.07$).

It is relevant to consider the substance P content of the bladders both in absolute terms and as a concentration (taking into account differences in bladder weight). If substance P is confined to nerves, the muscle hypertrophy and hyperplasia and increase in connective tissue elements in the bladder wall seen in obstruction may serve to "dilute" the density of the nerves. This may occur without any loss of nerve fibres, so that the total

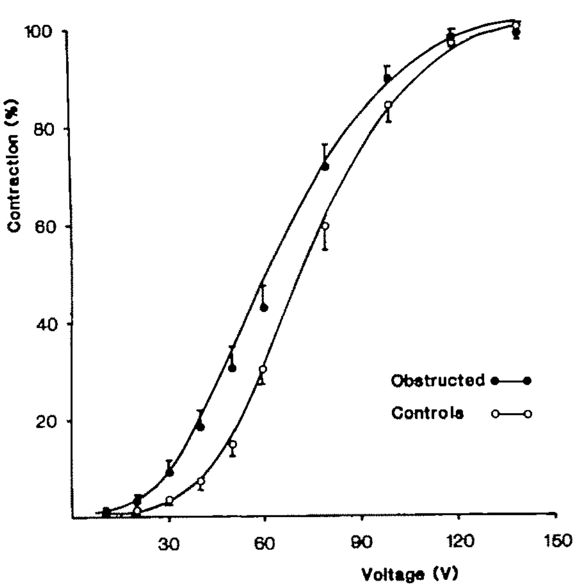

Fig. 6 Voltage response curves for muscle strips from obstructed (n = 14) and control (n = 10) rabbits. Contractions are expressed as a percentage of the maximum response obtained during the experiment. Values are means (±SEM) The computer generated best fit curves are shown, the curves did not differ significantly.

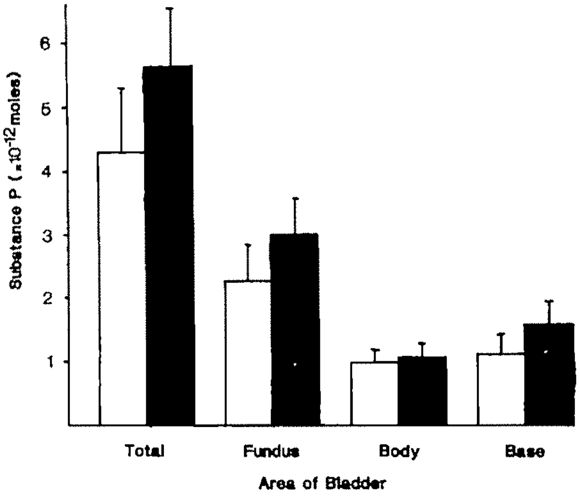

Fig. 7 Substance P content for obstructed bladders (n = 7, shaded bars) and control bladders (n = 5, white bars). Values are means (±SEM). There were no significant differences in substance P levels between the 2 groups

substance P content would remain unaltered but the concentration would fall. The results of the substance P assays are shown in Figure 7. The data illustrated give the absolute content of the peptide; no significant differences were observed between the 2 groups. For the obstructed group the total concentration was 0.79 (±0.14) × 10^{-12} moles/g and for controls 1.62 (±0.55) × 10^{-12} moles/g; these values were not significantly different.

Discussion

This study has demonstrated that the rabbit offers a useful animal model for studying the effects of chronic outflow obstruction on the innervation of the bladder. The success of the operative procedure in causing significant obstruction was confirmed by the urodynamic studies and by the macroscopic appearances of the bladders. Unfortunately, only half of the obstructed group of animals completed the 3-month study period; none of the rabbits that developed urinary retention completed the study. Other workers have observed a significant mortality rate following obstruction of the rabbit bladder neck (Brent and Stephens, 1975). Urinary retention was the major complication that led to animals being withdrawn from the study; some refinement to the surgical technique used to induce obstruction would be desirable for future studies.

The filling phases of the cystometrograms of the 2 groups of animals appeared similar; no alteration in early filling compliance was seen and there were no phasic contractions suggestive of detrusor instability. Studies of bladder outflow obstruction using the pig (Sibley, 1987) and, less convincingly, the rat (Malmgren *et al.*, 1987) have demonstrated contractions resembling those seen in patients with detrusor instability. It would appear that the rabbit does not exhibit this response to obstruction, although it is possible that the use of increment filling or pentobarbitone sedation may have masked any unstable bladder behaviour.

Urinary infection may alter detrusor function (Mayo and Hinman, 1976). In the present study, positive cultures were obtained from a similar proportion of rabbits in each group, suggesting that any effect should be balanced out. Furthermore, the organisms cultured were staphylococci in all but 1 case; these organisms are not usually associated with urinary infections in man and may represent contaminants. Contamination may have occurred during the urodynamic studies that were carried out a few days before the animals were killed.

The muscle strip studies demonstrated a number of differences between detrusor muscle from obstructed and control bladders. A striking degree of supersensitivity to acetylcholine was observed, coupled with reduced responses to stimulation of the intramural bladder nerves. This combination of results strongly suggests that a degree of detrusor denervation had occurred. Similar pharmacological results have been observed in studies of obstructed human and pig detrusor (Sibley, 1984, 1987); in these species, histological observation of post-ganglionic parasympathetic nerve loss provided supportive evidence of denervation (Gosling *et al.*, 1986; Speakman *et al.*, 1987). This finding means that the rabbit is a valuable additional animal model which can be used to study post-obstructive denervation; it is of particular potential value since it avoids some of the problems associated with the use of a large animal such as the pig.

The findings in the present study contrast with results reported by Levin *et al.* (1984). They examined the effects of short-term obstruction on the rabbit bladder and found that, 1 week after obstruction, supersensitivity to bethanechol could not be detected. Furthermore, the contractile properties of detrusor muscle strips were impaired. More recent studies by this group (Kato *et al.*, 1988) have examined the effect of mild outflow obstruction over a 2-week period. They found evidence of neuronal damage in these experiments using a whole bladder *in vitro* preparation. These findings suggest that the duration and severity of the obstruction determine the outcome in terms of the bladder's innervation and contractile mechanisms.

The rabbit detrusor contains both cholinergic and non-cholinergic transmitter systems. The proportion of the nerve-mediated responses that were atropine-resistant was found to be markedly variable from muscle strip to muscle strip. Because of this the reduction in the maximal atropine-resistant response seen in the obstructed group (15% compared with 26.8% for the control group) failed to reach significance, although responses at 30 Hz did differ significantly. The results suggest that obstruction may have more damaging effects on non-cholinergic transmitter systems than on cholinergic ones. It is not clear whether non-cholinergic transmitters are released from distinct non-adrenergic non-cholinergic nerves, as suggested by Burnstock *et al.* (1978), or are co-released from the cholinergic nerves. If there is a separate population of nerves, these fibres may be more sensitive to damage from the effects of obstruction than the cholinergic nerves. If there is co-release of neurotransmitters, then changes in the release, diffusion or muscle responsiveness might account for any differential reaction to obstruction.

Inhibitory mechanisms in the detrusor have not been clearly defined. It is of interest that one potential inhibitory system, that is the adrenergic sympathetic nerves acting via β-receptors, appears to show a significant reduction in inhibitory activity in the obstructed detrusor. This conclusion is based on the finding that isoprenaline shows reduced inhibitory activity against both nerve-mediated and carbachol-induced contractions of obstructed bladder muscle. The mechanism underlying this change is not clear but it may reflect an increased excitability of the detrusor. Another possibility is that the change has been brought about by an alteration in the populations of adrenoreceptors. Changes in the balance between α- and β-receptor activity were seen in the obstructed dog bladder by Rohner *et al.* (1978), who found that detrusor muscle strips from control animals all showed a β-receptor mediated relaxation response when exposed to noradrenaline. In contrast, 58% of strips from obstructed bladders contracted when exposed to noradrenaline (an α-receptor effect). It was suggested that this change could account for the development of the reduced compliance and instability that is seen in bladders whose outflow tract is obstructed. Norlén *et al.* (1976) showed that parasympathetic denervation of the feline bladder resulted in an alteration in the relationship between α- and β-receptors with a shift in the balance towards α-receptors. Similar changes are possible in the obstructed (and denervated) bladder. Reduced efficiency of inhibitory mechanisms may be one factor in the development of bladder instability. Attempts by the central nervous system to control the overactive bladder may be thwarted by damage to inhibitory pathways.

A more sensitive response to direct electrical stimulation of smooth muscle (as opposed to neurogenic stimulation) was observed in muscle strips from obstructed bladders, but the change did not quite reach statistical significance. Such a change was observed by Sibley (1984) in obstructed human detrusor but not in muscle from obstructed pig bladders. An increase in the sensitivity of smooth muscle to this type of direct stimulation is compatible with denervation. Lee *et al.* (1975) observed an increased sensitivity to direct muscle stimulation in denervated rat vas deferens.

The results of the measurement of the substance P content of the bladder showed no significant changes between obstructed and control bladders, either in the concentration of the peptide or in the absolute level. The substance P content of different areas of the bladder was also similar in both groups.

The average substance P content in the obstructed bladders was higher than in the control bladders, but the higher weights of the obstructed bladders meant that the mean concentration of the peptide was lower than for controls. It has been shown that a substantial amount of the substance P found in the bladder is contained in capsaicin-sensitive sensory nerves (Harrison, 1988). It would therefore appear that obstruction does not lead to significant damage to this category of neurone. This conclusion has to be made with some reservations because substance P may be present in sites other than sensory nerves and the levels of the peptide may alter for reasons other than neuronal loss. However, the findings in the obstructed rabbit bladder do suggest that there may be some selectivity in the pattern of nerve damage and that sensory fibres may be spared. The effect of outflow obstruction on the substance P content of the rat bladder was studied by Andersson *et al.* (1988). They found a significant increase in total bladder substance P levels but a reduction in substance P concentration. Unfortunately, interpretation of these results is difficult because of the more than 10-fold difference between the weights of the obstructed and control bladders.

This study has shown clear evidence of denervation in the rabbit detrusor that has been subjected to the effects of outflow tract obstruction. Furthermore, isoprenaline was seen to become less effective at inhibiting the activity of the muscle. Finally, there is evidence to suggest that some types of sensory nerve may be spared from the denervation process. The concept of selective denervation would therefore appear to be of considerable importance in determining the response of the bladder to outflow tract obstruction. Different patterns of nerve loss may explain the different responses of the bladder to obstruction; this can vary from failure of contractile mechanisms (and chronic retention of urine) to the severe overactivity that can be seen in some patients with detrusor instability.

Acknowledgement

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The Authors

S. C. W. Harrison, MA, MChir, FRCS, formerly Research Registrar in Urology, Addenbrooke's Hospital. Now Senior Registrar in Urology, Southmead Hospital, Bristol.

D. R. Ferguson, MD, University Lecturer in Pharmacology.

P. T. Doyle, FRCS, Consultant Urologist.

Requests for reprints to: S. C. W. Harrison, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

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Initial Evaluation and Response Criteria for Patients with Superficial Bladder Cancer

Report of a Workshop*

M. S. SOLOWAY, W. M. MURPHY, D. E. JOHNSON, G. M. FARROW, D. F. PAULSON and M. B. GARNICK

Departments of Urology and Pathology, University of Tennessee, Memphis; Department of Urology, M. D. Anderson Hospital, Houston; Department of Pathology, Mayo Clinic, Rochester; Division of Urology, Duke University Medical Center, Durham; Genetics Institute, Boston, USA

The term "superficial" has been applied to bladder neoplasms representing a wide spectrum of pathological grades and clinical stages, including benign lesions such as transitional cell papillomas and aggressive tumours such as transitional cell carcinomas which have invaded into the lamina propria. While it must be recognised that superficial bladder neoplasia does not represent a distinct entity, use of the term emphasises the widespread recognition among urologists that the great majority of bladder neoplasms, regardless of their degree of cellular anaplasia, do not become clinically aggressive, *e.g.* metastasise, until they have invaded the muscular wall. Furthermore, the location of these lesions makes them amenable to non-aggressive types of treatment such as resection and fulguration and intravesical chemotherapy.

Despite the variety of urological neoplasms which can present as superficial lesions, our experience indicates that there is considerable agreement in both the pathological and urological communities regarding the biological potential of these tumours and their clinical evaluation and treatment. Urologists, oncologists and those involved in co-operative trials would all benefit from a consensus on the "standard" initial evaluation and follow-up schema for patients with bladder cancer. The following discussion represents a consensus among individuals with expertise in this group of tumours. It is intended to provide useful information to those who would welcome guidance in this area. The conclusions are consistent with guidelines proposed by the first Consensus Conference on Bladder Cancer (Niijima *et al.*, 1986; Soloway *et al.*, 1986).

Initial Evaluation of Patients with Superficial Bladder Cancer

Superficial bladder neoplasia must be considered in any adult who complains of haematuria or symptoms indicating irritation of the lower urinary tract. In such cases a random voided urine specimen should be obtained prior to endoscopy. If a bladder neoplasm is suspected or established at the time of cystoscopy, the urinary specimen can be sent for cytological examination. In addition to an intravenous urogram, a thorough evaluation of the lower urinary tract should be performed and any lesions should be resected for histological examination. A thorough examination will require anaesthesia, either general, spinal or epidural.

The need for pathological examination of specimens obtained from the urinary bladder in patients suspected of superficial bladder neoplasia is well established. While the histological examination of tissue specimens to determine the presence of neoplasia, its degree of cellular anaplasia (grade) and its level of invasion (stage) hardly requires justification, cytological examination of 1 or more urinary specimens should not be neglected. Discordant results, *i.e.* the appearance of high grade malignant cells in the urinary specimen but only low grade papillary lesions in the histological material, are not uncommon during follow-up and may occur even at the initial evaluation, especially if the patient has a history of bladder cancer at the time when he is newly referred to the examining

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*Summary of Workshop on Response Criteria for Superficial Bladder Cancer held in Memphis, April 1989 urologist. In such cases, endoscopically invisible carcinoma *in situ* (CIS) involving the bladder, prostatic urethra or upper urinary tracts is not infrequent and its discovery is important, since the presence of CIS may alter treatment.

Three types of urinary specimen are commonly obtained. Random voided urine and "cystoscopic" urine (obtained when the instrument is first introduced into the bladder) yield cells of similar preservation and morphology. Although the cellular elements in these preparations may not be optimally preserved, malignancy can be recognised by experienced observers and voided urine/cytoscopic urine occasionally yields tumour cells not present in simultaneously obtained bladder washings (Murphy *et al.*, 1981). Obtaining these specimens prior to cystoscopy has the further advantage of not disturbing the bladder mucosa with vigorous lavage. Bladder washings should be performed whenever instrumentation is otherwise required in patients suspected of harbouring a bladder neoplasm. Ordinarily, bladder washing specimens contain more and better preserved urothelial cells than voided urine. Papillary clusters are more frequently present, however, and these clusters may confound the interpretation of low grade neoplasms unless the cytopathologist is aware of this pitfall and uses other, more significant cytological criteria for evaluation (Murphy *et al.*, 1984). All 3 types of urinary specimen may yield valuable information and there is no need for the urologist or the pathologist to develop distinct preferences for any one type.

In patients suspected of bladder neoplasia, initial urological evaluation should include bimanual examination as well as endoscopy with biopsy and/or complete resection of any visible lesion. Bimanual examination is important to exclude large, deeply invasive cancers as well as to provide the patient with a thorough pelvic examination. In the male, bimanual examination should be performed with one finger in the rectum and the other hand on the suprapubic area. It is helpful if the clinician first uses the index finger of one hand in the rectum and the opposite hand on the abdomen, forcing the bladder and pelvic structures downward. The hands are then reversed and the procedure repeated. Examination of the prostate is particularly important since there is a high incidence of prostate adenocarcinoma among patients with bladder neoplasms. Any palpable abnormality should be biopsied. In the female, 2 fingers should be placed in the vagina with the other hand on the suprapubic area to allow palpation of the bladder and adjacent structures. It is helpful to repeat the manoeuvre after switching hands.

The technique of endoscopic evaluation has been well described. Sufficient lenses are required to examine the entire urethra and bladder. Overdistension of the bladder should be avoided since it may lead to rupture of small blood vessels and produce haemorrhage which may mask subtle mucosal abnormalities. Biopsy and/or transurethral resection of suspicious areas or bladder tumours can be facilitated by using a continuous flow resectoscope. The continuous flow resectoscope allows the bladder volume to be stabilised during resection and may reduce the chance of perforation. If the tumour can be safely resected in its entirety, the urologist should do so. The tumour should be resected in such a way as to include at least some muscle if there is any possibility that the neoplasm has extended beyond the basement membrane of the mucosa. Following tumour resection, haemostasis can be assured with the use of a roller electrode. The neighbouring urothelium should be fulgurated, a procedure facilitated by using the roller electrode. Following resection of all visible tumour, a 70° lens should be used to examine the bladder, thus ensuring that all tumour has been removed, if possible.

Urologists experienced in detection and monitoring of patients with superficial bladder cancer have found that a bladder diagram is extremely useful and should be completed in every case. This diagram, which may be a formal design used by all urologists in the hospital or a simple hand-drawn picture on the progress note, should identify the location of all tumours and the site of any biopsies performed. Pertinent landmarks should be noted on the diagram.

Cold cup or transurethral resection mucosal biopsies are suggested in certain instances. Any portion of the urothelium which is suspicious for cancer should be biopsied and the site of the biopsy indicated on the pathology requisition form. Mucosal biopsies are necessary when a partial cystectomy is being contemplated. Mucosal biopsies are also indicated when the cytology reveals the presence of a high grade tumour but the endoscopy suggests only papillary tumours of apparent low grade.

The prostatic urethra should always be carefully examined and, in certain instances, a transurethral resection biopsy should be performed. Indications for a prostatic urethral biopsy include: (1) abnormal appearance suggestive of carcinoma; (2) presence of high grade tumour cells in a cytological specimen but only low grade tumour in the endoscopy/histology material; (3) patients with multifocal carcinoma *in situ* of the urinary bladder; (4) patients who are candidates for a continent diversion to the urethra. Biopsies from the prostatic urethra should provide sufficient material not only to determine the presence of a carcinoma but to evaluate involvement of the prostatic ducts and stroma. Lastly, all specimens submitted to the pathology laboratory should be appropriately labelled as to location. A history of previous therapy should also be noted, *e.g.* intravesical therapy or radiation.

Pathological Reporting

The urologist will make a decision regarding additional therapy based upon the information obtained from pathological analysis. It is therefore incumbent upon the pathologist to provide a report containing essential information regarding the urothelial neoplasm. Guidelines for pathological reporting of histological specimens from patients with bladder cancer have been summarised by a recent task force (Pathologist, 1986). At a *minimum*, each histology report should document the type of neoplasm, provide the grade if the tumour is transitional cell, describe the depth of invasion and state whether or not muscle is present in the specimen. Other information might include: (1) the pattern of growth (papillary or infiltrating); (2) vascular invasion; (3) the character of invasion (broad front or tentacular).

The cytology report should include: (1) the presence of neoplastic cells and (2) a clear distinction of cytological grade (urologists will otherwise assume that a "positive" cytology means high grade). Other helpful information might include the presence of dysplastic cells, regenerative/reparative cells and evidence of Cytoxan effect. Other therapeutic effects and inflammation can be reported but are of little benefit to the urologist or the patient.

The participants of the workshop considered the subject of flow cytometry at some length. While there may be advantages to techniques which evaluate the amount of DNA present in neoplastic cells or estimate the S-phase component, the use of these techniques as an independent diagnostic variable was considered primarily a research endeavour. In the future, cytometry and other techniques may yield invaluable information for predicting the biological behaviour of urothelial cancers in terms of risk of recurrence and progression. Indeed, some pathologists have considered the sensitivity and specificity of flow cytometry to be superior to that of visual cytology (Gustafson *et al.*, 1982; Murphy *et al.*, 1986; Badalament *et al.*, 1987; de Vere White *et al.*, 1988). The amount of data currently available is insufficient to recommend these procedures as standard practice, however.

Computed tomography is to be performed only if there is some suggestion based upon physical examination, cystoscopic findings, or the pathology that the patient has a T3 or T4 bladder cancer. For patients with apparent superficial bladder neoplasia (Ta, Tcis, T1) or even for those with T2 lesions (superficial muscle invasion), computed tomography rarely provides important information.

Subsequent Evaluations

After the diagnosis of superficial bladder neoplasia has been established, patients may be monitored by endoscopy with or without histology but it should be emphasised that urinary cytology, using voided or bladder irrigation specimens, is an essential part of any monitoring system. The workshop participants recommended at least 1 urinary cytology within the first month following initial tumour resection (Table). Based upon the results of pathological and clinical studies performed at the time of primary treatment as well as the results of the initial cytological specimen obtained after resection, patients can be categorised into either low risk or high risk groups. The risk is primarily referable to tumour progression in grade or stage.

Low risk patients

Patients at low risk for progression (not necessarily recurrence) or superficial bladder neoplasia have the following characteristics:

(1) Single or multiple clinical stage Ta, grade I transitional cell carcinoma (papilloma) (Pocock

Table Flow Sheet for Monitoring Patients with Superficial Bladder Neoplasia

	Low risk (months)				*High risk (months)*		
	1	*3*	*6*	*Every 6*	*1*	*3*	*6*
Endoscopy*		×		×		×	×
Cytology	×	×	×	×	×	×	×
Urine analysis	×	×	×	×	×	×	×

*Biopsies as indicated by endoscopic and cytological findings.

et al., 1982; Heney *et al.*, 1983; Morrison *et al.*, 1984; Torti *et al.*, 1987).

(2) Cytology negative for high grade tumour cells both at initial evaluation and during the post-resection monitoring (Muller *et al.*, 1985).

These patients should be followed up with urinary cytology performed within the first 3 months. An endoscopic examination should be performed 3 months after initial treatment. If no tumour is identified endoscopically and the cytology is negative for high grade tumour cells, endoscopy need not be performed every 3 months thereafter. The most appropriate interval is unknown but the workshop participants were comfortable with 6 months. It should be recognised that this recommendation represents a departure from the advice given in many previous reports. Patients who remain free of disease, documented endoscopically, histologically and cytologically for at least 4 years, can be followed up with yearly evaluations. A routine urine analysis looking for microscopic haematuria is a valuable adjunctive procedure in follow-up (Meuleman and Delaere, 1988). As long as patients remain asymptomatic with negative urine analysis and cytology, intravenous urography is not necessary. Patients who develop positive cytology for high grade tumour cells or who have histological lesions of transitional cell carcinoma grades II or III (WHO system) during monitoring should be placed in the high risk group.

High risk patients

Patients whose initial neoplasms are histological grades II or III (WHO system), carcinoma *in situ*, invasive into the lamina propria regardless of cytological grade, and patients who have positive cytology for high grade tumour cells regardless of histological grade of their tumour, are at high risk for progression. Following initial tumour resection, these patients should be monitored with urinary cytology performed within the first month after treatment. If the cytology is negative for high grade tumour cells, the first follow-up endoscopy can be performed at 3 months. If no tumour is present either histologically, endoscopically or cytologically, a subsequent evaluation should be performed at 3 months. If the studies remain negative at this second 3-monthly follow-up, patients can be followed at 6-monthly intervals. Since it can be a non-invasive test, is relatively inexpensive and is accurate for detecting high grade tumour, urinary cytology should be performed more frequently than every 6 months whether or not patients are being scheduled for endoscopy. Intravenous urography is not required in this group of patients as long as the clinical and pathological studies remain negative and the patient is asymptomatic. As with the low risk patients, regular urine analysis looking for microscopic haematuria is a valuable monitoring procedure.

Patients whose initial cancers have invaded the lamina propria (T1) and are of high cytological grade (WHO III) are at especially high risk for progression (Jakse *et al.*, 1987; Abel, 1988; Rubben *et al.*, 1988). Although most of these individuals can undergo apparently successful transurethral resection, follow-up cytology often reveals residual high grade tumour cells. In such cases there are 3 alternatives: (1) intravesical therapy; (2) cystectomy; (3) repeat endoscopic examination following review of the initial histological material to determine the site and extent of any remaining neoplasm.

Advocates of a repeat resection believe that it minimises understaging and has a better chance of rendering the patient disease-free. If high grade transitional cell carcinoma appears in biopsies from the prostatic urethra, the standard treatment is cystoprostatectomy (and urethrectomy). If the neoplasm is confined to the mucosa with no extension into the prostatic acini, ducts or stroma at repeat endoscopy, some investigators have suggested transurethral resection followed by intravesical therapy (Hillgard *et al.*, 1988; Bretton *et al.*, 1989). Unfortunately, long-term follow-up information is not available to determine the validity of this recommendation. Papillary low grade tumours confined to the prostatic mucosa can be treated with transurethral resection with or without subsequent intravesical therapy.

Intravesical therapy may be in the form of chemotherapy (thiotepa, mitomycin C or doxorubicin hydrochloride) or BCG. This treatment can be considered for those few individuals with extensive but superficial lesions which are not amenable to transurethral resection. It is also appropriate for patients with positive cytology but no obvious neoplasm in their bladder, upper tracts or prostatic urethra. Intravesical therapy can be used in cases where recurrences are frequent but the tumours are low grade and superficial. In these instances, therapy is considered prophylactic and the clinician weighs the benefits of avoiding or delaying a subsequent endoscopic resection against the toxicity, cost and additional catheterisations required for placement of the intravesical agent. It should be recognised that whereas intravesical therapy will usually decrease the rate and number of recurrences, it may not alter the ultimate outcome of the disease.

Intravesical therapy often produces abnormal nuclear changes in superficial urothelial cells. These cells lack high nuclear cytoplasmic ratios and should not be considered in the cytological diagnosis of cancer even though their nuclear changes, when viewed alone, may appear anaplastic (Murphy *et al.*, 1981). In especially difficult cases, the best course of action may be to repeat the cytology after 1 month without therapy or to solicit a second opinion.

Criteria for Response following Intravesical Therapy

If a patient has tumour remaining in the bladder after resection or a cytology positive for high grade tumour cells and receives a 6 to 8-week course of intravesical therapy for treatment, the response is evaluated 12 weeks after the initial endoscopy. A complete response must include the following criteria: (1) no tumour at endoscopy; (2) no tumour cells on cytology; (3) no neoplasia in biopsies. Using these criteria, patients with positive cytologies with or without biopsy confirmation should be considered treatment failures. If papillary tumours are identified, they should be confirmed histologically. In some cases the cytology may be negative even though a papillary tumour exists. For the purpose of evaluating intravesical therapy, atypia and dysplasia do not constitute positive specimens, either cytologically or histologically. A partial clinical response is not valid.

Patients receiving intravesical therapy for prophylaxis are monitored according to their disease-free intervals. The term "complete response" is not appropriate for patients being treated for prophylaxis. Time to recurrence, time to progression and the recurrence rate are appropriate end points (Herr *et al.*, 1987, 1988; Kalish *et al.*, 1987).

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The Authors

M. S. Soloway, MD, Professor, Department of Urology, University of Tennessee, Memphis.

W. M Murphy, MD, Professor, Department of Pathology, University of Tennessee, Memphis.

D. E. Johnson, MD, Professor, Department of Urology. M.D. Anderson Hospital, Houston.

G. M. Farrow, MD, Professor of Pathology, Mayo Medical School, Mayo Clinic, Rochester.

D. F. Paulson, MD, Chairman, Division of Urology, Duke University Medical Centre, Durham.

M B Garnick, MD, Vice President, Clinical Development, Genetics Institute, Boston.

Requests for reprints to M S Soloway, Department of Urology, University of Tennessee, 956 Court Avenue, Box 10, Memphis, Tennessee 38163, USA.

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Reduced Bladder Capacity in Patients Receiving Intravesical Chemoprophylaxis with Mitomycin C

A. EIJSTEN, H. KNÖNAGEL, E. HOTZ, H. P. BRÜTSCH and D. HAURI

Department of Urology, University Hospital, Zurich, Switzerland

Summary—After complete resection of superficial bladder carcinoma (Tis-2, G1–3), 75 patients were treated prophylactically with either 20 or 30 mg mitomycin C. Six patients developed a substantial reduction in bladder capacity (less than 200 ml). In 2 patients radical cystectomy of an otherwise tumour-free fibrotic bladder was necessary. The results of long-term treatment (2 years) suggest that reduced bladder capacity correlates with the cumulative dosage of mitomycin C.

Introduction

In patients with superficial bladder carcinoma, the intravesical application of cytotoxic or immunogenic agents (either as treatment for those with residual tumour or as prophylaxis for those without residual tumour following a second transurethral staging) has become widely accepted. The use of a variety of agents and regimens in the last decade has made it difficult to assess their efficacy (Morales *et al.*, 1981; Kurth *et al.*, 1984; Herr *et al.*, 1987; Stricker *et al.*, 1987; Huland *et al.*, 1988; Rübben *et al.*, 1988). The potential toxicity and risk of severe local side effects of these agents have seldom been discussed. During the long-term use of prophylactic mitomycin C we frequently encountered the problem of a severe reduction in bladder capacity and this report focuses on this specific complication.

Patients and Methods

Starting in 1983, we carried out 2 consecutive studies on long-term intravesical chemoprophylaxis with mitomycin C (KYOWA). Patients with normal bladder capacity following complete resection of bladder carcinoma (Tis-2, G1–3) and negative transurethral staging 3 to 4 weeks later were included. The studies differed with regard to the dose of mitomycin C (30 mg in study 1, 20 mg in study 2) and mean follow-up (Table 1); in all other respects the studies were comparable.

The drug was instilled into the empty bladder by catheter and retained for 1 h. The first 2 instillations were performed within the first week after negative transurethral staging; subsequent instillations were carried out every second week during the first 6 months, once a month for the next 6 months and then every second month in the second year. Cystoscopy and cytological examination of the urine and measurement of bladder capacity were performed every third month.

Patients whose bladder capacity decreased to less than 200 ml underwent further examination.

Results

Table 1 gives details of patients in both study groups. The mean follow-up period shows a

Table 1 Details of Patients

	Study 1 (30 mg mitomycin C)	*Study 2 (20 mg mitomycin C)*
No of patients	50	26
Males	40 (80%)	21 (81%)
Females	10 (20%)	5 (19%)
Median age (years)	59 (33–84)	63 (41–84)
Mean follow-up (months)	40 (10–54)	18 (3–29)
Recurrent tumour at inclusion	28 (56%)	11 (42%)
Deaths	4 (8%)	3 (12%)

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Table 2 Bladder Capacity, Treatment and Results

	Study 1 (30 mg mitomycin C) (n=50) (%)	*Study 2 (20 mg mitomycin C) (n=26) (%)*	*Study 1+2 (n=76) (%)*
Bladder capacity <200 ml	10 (20)	7 (27)	17 (22)
Bladder capacity <100 ml	4 (8)	1 (4)	5 (7)
Discontinuation of treatment	6 (12)	4 (15)	10 (13)
Improvement in bladder capacity to >200 ml	4 (8)	1 (4)	5 (7)
Cystectomy and ileal loop diversion	2 (4)	0	2 (3)

significant difference because of the later initiation of the second study. Only 2 of 7 deaths were related directly to bladder carcinoma, both patients having had G2 tumours.

Of 76 patients, 17 (22%) developed a reduction in bladder capacity to less than 200 ml and in 5 cases it was less than 100 ml. Four of these 5 patients were in study 1 and treatment was discontinued immediately in all 5 (Table 2). Symptoms developed gradually and the decision to stop treatment was taken at a mean dose of 420 mg mitomycin C (range 270–570) in study 1 and 360 mg (range 320–400) in study 2. Bladder capacity improved in 4 of 10 patients in study 1 and no discontinuation of treatment was necessary in 3. The bladder capacity of the other 6 patients remained below 200 ml and in 2 of them the contraction was so pronounced that radical cystectomy and ileal loop diversions were necessary 11 and 17 months after initiation of intravesical mitomycin C therapy. In both cases histological examination revealed a tumour-free fibrotic bladder; both patients are still alive 34 and 21 months after cystectomy. Histological examination of biopsies from a further 4 patients revealed only unspecific erosive cystitis. We cannot comment on the 7 patients with reduced bladder capacity in study 2 except for a 45-year-old patient whose bladder capacity returned to normal after finishing treatment. Endoscopic examination of his bladder shortly before the end of treatment revealed the typical signs of chemocystitis and a capacity of 60 ml. Two of the remaining 6 patients died of disease not related to bladder carcinoma; the other 4 have not yet completed their course of treatment.

Discussion

Of 76 patients undergoing a 2-year course of intravesical chemoprophylaxis with mitomycin C, 17 (22%) developed a decrease in bladder capacity to less than 200 ml. In at least 6 patients (8%) the reduction was permanent and in 2 cases cystectomy with supravesical urinary diversion was mandatory. We recently performed cystectomy with a continent ileal S-pouch to the prostatic urethra on another patient with severe bladder contraction (capacity 50 ml). The 72-year-old man had received intravesical chemoprophylaxis with mitomycin C in accordance with the regimen in study 1 at another hospital. The fibrotic bladder showed no sign of residual carcinoma. A review of the literature has revealed no comparable figures on bladder contraction in connection with chemoprophylaxis and only single case reports could be found. Baker *et al.* (1987) described a 62-year-old woman whose bladder contraction eventually led to cystectomy and ileal loop diversion. She had 14 applications of 40 mg mitomycin C in 10 months shortly after unsuccessful treatment of recurrent T1 G1 superficial bladder carcinoma with thiotepa. Reviewing the case histories of 29 patients who had undergone 1 year's treatment with mitomycin C (18 applications of 40 mg), Nissenkorn *et al.* (1981) found only moderate cystitis in 3 patients. In a study similar to our second study (M1 branch), Huland *et al.* (1988) found chemocystitis to be the leading complication in 19% of 179 patients but severe reduction in bladder capacity was not recorded. The only difference between regimens in this study and our own was the interval of 4 to 6 weeks between tumour resection and initiation of prophylaxis.

Our results and the literature review lead to the following conclusions. The short interval between the second resection and the first intravesical application of mitomycin C may increase local toxicity because of the recent deep lesions to the bladder wall, although early initiation of prophylaxis in respect of the underlying malignant disease may be very important. Long-term prophylaxis, especially with high doses of mitomycin C, may cause local toxicity and thus a higher risk of bladder fibrosis. Based on these possibilities, the indications for and duration of intravesical chemoprophylaxis should be reassessed. We agree with Rübben (1988) that primary low risk tumours (Ta G0–4, T1 G1–2) should not receive intravesical chemoprophylaxis.

The duration of prophylactic treatment should be limited to 6 to 12 months, since the superiority of long-term regimens has not yet been proven (Herr *et al.*, 1987; Huland *et al.*, 1988). In agreement with the protocols of Huland *et al.* (1988) and Denis *et al.* (1987), the interval between the last resection and the first intravesical application could probably be longer without any loss of efficacy of treatment.

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The Authors

A. A. Eijsten, MD, Urologist.
H. H. Knönagel, MD, Senior Resident.
E. Hotz, MD, Urologist.
H. P. Brütsch, MD, Surgeon.
D. Hauri, MD, Professor and Head of Department of Urology.

Requests for reprints to· A. Eijsten, Bahnweg 18, CH-8706 Meilen, Switzerland.

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Variations in Urethral and Bladder Pressure during Stress Episodes in Healthy Women

P. THIND, G. LOSE, LISBETH JØRGENSEN and H. COLSTRUP

Department of Urology, Rigshospitalet, Copenhagen, Denmark

Summary—Pressure variations in the urethra and bladder during stress episodes and their time separations were investigated in 30 healthy female volunteers. The pressure was measured by means of a double microtip transducer catheter with the distal sensor in the bladder and the proximal sensor at the bladder neck, the mid-urethra and the distal urethra. In advance of the pressure spike during cough a pressure rise was demonstrated in the bladder and at all 3 sites of measurement in the urethra. The urethral pressure increments preceding and following the pressure spike were statistically significantly higher in the mid-urethra than the corresponding bladder pressures. This active urethral pressure generation in the mid-urethra and distal urethra was initiated 200 ms before the bladder pressure began to rise. The pressure in the urethral high pressure zone was higher than the bladder pressure in all cases. Passive pressure transmission to the urethral high pressure zone can take place only insignificantly due to a continuous higher pressure inside the urethra than in the bladder and due to the location of the high pressure zone in the demarcation of the abdominal cavity. It was concluded that the urethral pressure rise in the high pressure zone during stress episodes is mainly generated actively by intra- and/or peri-urethral structures.

Continence of urine is maintained by a positive urethral closure pressure generated by the peri- and intra-urethral structures (Enhörning, 1961; Asmussen and Ulmsten, 1983; Caine, 1986). During stress episodes the urethral closure pressure remains predominantly positive in healthy volunteers and negative in women with genuine stress incontinence (Asmussen and Ulmsten, 1983; Constantinou, 1985). It has been claimed that the pressure increase in the urethra during stress episodes is produced by a combination of passive pressure transmission from the abdominal cavity and active pressure generation by peri- and intra-urethral structures (Enhörning, 1961; Fossberg and Beisland, 1982; Asmussen and Ulmsten, 1983; Constantinou, 1985; Caine, 1986). However, the pressure variations in the urethra and the bladder during stress episodes are complex (Fig.) and the exact role of passive and active mechanisms remains unclear.

In this study the variations in urethral and bladder pressures and their time separations have been investigated.

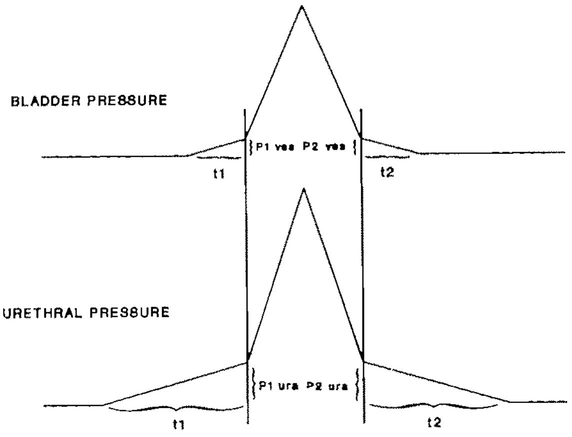

Fig. Schematic drawing of bladder and urethral pressure variations during cough episode Vertical lines indicate the beginning and end of pressure spike. The marked pressures and times are defined in the text

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Materials and Methods

Thirty healthy female volunteers aged 25 to 74 years (median 42) were studied. None of the women had previously undergone urological or gynaecological surgery and they had no gynaecological or urological complaints. The pressure measurements were performed by means of a specially designed double microtip transducer catheter (Lose *et al.*, 1986, 1988). The distal sensor was placed in the bladder. The proximal sensor was placed in the urethra and covered with a 1.5-cm water-filled rubber balloon with a fixed cross-sectional area of 20 mm^2. The balloon was used to avoid artificial pressure generation due to secondary forces from bending of the catheter caused by its stiffness and weight (Plevnik *et al.*, 1985). Pressure recordings with the proximal sensor covered and uncovered were checked in a pressure chamber and found to be identical (Lose *et al.*, 1988).

The women were examined in the supine position with an empty bladder. Measurements were performed (1) at the bladder neck (0.75 cm from the urethrovesical junction), (2) mid-urethrally (in the high pressure zone) and (3) distally in the urethra (0.75 cm from the external meatus). At each site of measurement in the urethra the women were asked to cough 3 times. The most efficient cough was used for calculation.

Informed consent was obtained from the women and the study was approved by the regional ethical committee.

Methods, definitions and units of measurements conform to the standards recommended by the International Continence Society except where specifically noted. The following definitions during cough were used in this study (Fig.):

P_{cough}: Maximum pressure increase during cough.

P_1: Pressure increase at the onset of pressure spike during cough.

P_2: Pressure increase at the end of pressure spike during cough.

t_1: Time from the onset of pressure increase to the onset of pressure spike during cough.

t_2: Time from the end of pressure spike to the end of pressure increase during cough.

Pressure spike: Pressure changes from the beginning of straight incline of bladder pressure to the end of straight decline of bladder pressure during cough.

The bladder and urethral pressures were registered, processed and displayed on a 6-channel recording system (Disa Urosystem 21F 16 2100). The frequency response of the amplifying system was 100 Hz, paper speed 15 mm/s.

Statistical analysis was based on standard nonparametric methods using the Wilcoxon and Pratt's test or the Friedmann test to analyse differences between 2 or more sites of measurement in the urethra respectively. $P<0.05$ was considered statistically significant.

Results

P_{cough}, P_1 and P_2 are presented in Table 1. P_1 and P_2 were significantly higher in the mid-urethra compared with the corresponding pressures in the bladder; t_1 and t_2 are given in Table 2. The pressure increased significantly earlier at all 3 sites of measurement in the urethra compared with the bladder. The pressure increased mid-urethrally and distally in the urethra 200 ms before the pressure rose in the bladder. Mid-urethrally, all women had positive closure pressures during the cough episodes. The onset of and the end of the pressure spikes as well as the peaks of the pressure spikes were in all measurements without time separation between the bladder and urethra.

Table 1 Pressure Changes During Cough in 30 Healthy Female Volunteers

	Site of measurement			
(cmH_2O)	*Bladder*	*Bladder neck*	*Mid-urethra*	*Distal urethra*
P_{cough}	64 (45–82)	65 (43–83)		
	63 (52–86)		65 (43–83)	
	65 (45–77)*			39 (20–52)*
P_1	10 (7–15)	10 (9–15)		
	10 (9–10)†		14 (10–20)†	
	11 (7–15)			12 (8–19)
P_2	15 (11–20)	15 (10–20)		
	10 (8–12)†		14 (10–15)†	
	10 (9–14)			9 (6–14)

*$P<0.01$. †$P<0.05$.
Values are median with the 25th and 75th percentile in parentheses

Discussion

This study has demonstrated a pressure rise in both the urethra and bladder preceding and following the pressure spike during cough episodes, and the pressure increments were significantly greater in

Table 2 Duration of Pressure Increment in Bladder and Urethra Preceding (t_1) and Following (t_2) Pressure Spike during Cough Measured in 30 Healthy Female Volunteers

	Site of measurement			
(ms)	*Bladder*	*Bladder neck*	*Mid-urethra*	*Distal urethra*
t_1	100 (100–250)†	300 (200–400)†		
	200 (120–200)*		400 (250–550)*	
	200 (170–450)†			450 (300–475)†
t_2	300 (150–400)	550 (400–1000)		
	200 (100–350)*		400 (300–950)*	
	200 (100–350)			350 (275–625)

*P<0 01. †P<0 05.
Values are median with the 25th and 75th percentile in parentheses.

the mid-urethra than in the bladder. The urethral pressure started to rise before the bladder pressure and was initiated in the mid-urethra and distal urethra followed by the bladder neck before the bladder pressure began to rise. This is consistent with previous studies (van der Kooi *et al.*, 1984; Constantinou, 1985).

The study was performed using a double microtip transducer catheter, with the urethral sensor covered by a water-filled balloon. The length of the balloon may influence the results, especially in the distal part of the urethra where the sites of measurement, the high pressure zone and 0.75 cm from the external meatus, are close to each other. This means that the measurements from these 2 urethral sites may in part reflect the same. Measurements in the bladder neck and mid-urethra can, however, be regarded as separate, since the distance between the 2 sites is significantly longer than the length of the balloon. Comparison of measurements from the 3 urethral sites should be made cautiously because the values were obtained during separate cough episodes due to the method, and because the values of P_1 and t_1 may vary according to the type of cough. Differences between urethra and bladder parameters may, however, be considered reliable as they were measured during the same cough episodes.

The urethral pressure elevation preceding and following the increase in bladder pressure is interpreted as an active pressure generation by the peri- and/or intra-urethral structures tending to preserve a positive urethral closure pressure (van der Kooi *et al.*, 1984). Sneezing produces nearly the same pressure increase in the urethral high pressure zone in dogs with an open and closed abdomen, which means that pressure generation in the urethral high pressure zone during stress episodes is predominantly active (Thüroff *et al.*, 1982). On the other hand, passive pressure transmission from the abdominal cavity to the urethra can be demonstrated in animals and patients that have been given curare using the Credé manoeuvre. The magnitude of this passive pressure transmission declines distally in an almost linear fashion (Heidler *et al.*, 1987; Massey *et al.*, 1987; Thüroff *et al.*, 1987). However, it cannot be concluded from these results that passive pressure transmission and active pressure generation are co-operating to sustain a positive urethral closure pressure during active stress episodes. Furthermore, passive pressure transmission inside the urethra can only take place to an area of lower pressure. In this study, the urethral pressure in the high pressure zone was always higher than the bladder pressure. Passive pressure transmission outside the urethra is strongly reduced at the high pressure zone because of its location in the demarcation of the abdominal cavity. Pressure transmission from the abdominal cavity to the urethral high pressure zone may take place due to leverage by stretching the pelvic floor (Heidler *et al.*, 1979). Such an arrangement will, however, cause a delay which was not measurable in this study.

In conclusion, during a stress episode in healthy women the urethral pressure variations in the high pressure zone are mainly actively generated by the intra- and/or peri-urethral structures.

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The Authors

P. Thind, MD, Research Fellow

G. Lose, MD, Senior Registrar, Specialist in Obstetrics and Gynaecology.

Lisbeth Jørgensen, MD, Senior Registrar.

H. Colstrup, MD, Senior Registrar, Specialist in Urology

Requests for reprints to: P. Thind, Department of Urology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.

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In vitro Evaluation of the Pollen Extract, Cernitin T-60, in the Regulation of Prostate Cell Growth

F. K. HABIB, MARGARET ROSS, A. C. BUCK, L. EBELING and A. LEWENSTEIN

University Department of Surgery (WGH), Western General Hospital, Edinburgh; Department of Urology, Royal Infirmary, Glasgow; Cernitin S.A., Lugano, Switzerland

Summary—Nine human-derived cancer and non-cancer continuous cell lines were employed to evaluate the relative *in vitro* activity of the pollen extract, Cernitin T-60. Responses of the cell lines to the drug were assessed by measuring growth and cell survival as determined by cell count. The results demonstrated that of the 9 continuous cell lines tested, only those derived from the human prostate were growth inhibited by the pollen extract, whereas the non-prostate derived cells exhibited variable degrees of resistance to the T-60. The selectivity of the drug for the prostate cell lines was even more pronounced in the hormone-independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells.

In spite of the considerable advances in our understanding of the processes leading to the growth and proliferation of the human prostate, the management of prostate diseases still remains a major clinical problem (Chisholm, 1989). Cancer of the prostate is the second most common cause of death due to cancer in males in the United Kingdom (Cancer Research Campaign, Factsheet 10.1, 1988) and the death rate is increasing. Clearly, the traditional forms of treatment such as surgery at the primary site, orchiectomy, hormone treatment and radiation are not as effective as Huggins might have originally perceived (Huggins and Hodges, 1941) and there is now every reason to find an alternative form of treatment.

Recently, there have been several reports suggesting that the pollen extract, Cernilton, is an effective agent in the treatment of prostate disease (Ito *et al.*, 1986; Buck *et al.*, 1989). The pollen extract is a preparation produced by AB Cernelle in Sweden and is essentially a microbial digestion of a mixture of pollens which have been extracted first in water and subsequently with an organic solvent (Kimura *et al.*, 1986).

In an attempt to assess the selectivity and specificity of these pollen extracts, we undertook a number of experiments to compare the *in vitro* activity of Cernilton towards a wide range of human-derived cancerous and non-cancerous continuous cell lines of prostate and non-prostate origin. We confined our experiments to the water soluble fraction T-60 component, which accounts for approximately 60% of the pollen extract. In addition, we also undertook a few experiments on benign hyperplastic prostates to test the impact of the pollen extract on testosterone metabolism and the binding of androgens to their receptors.

Materials and Methods

Chemicals

Cernitin T-60 was a gift from AB Cernelle, Helsingborg, Sweden.

Tissues

Specimens of benign prostatic hyperplasia (BPH), obtained by transurethral resection, were transferred to the laboratory and either used immediately or snap frozen in liquid nitrogen and stored at −70°C.

Cell cultures

The epithelial and fibroblastic cell lines were all derived from human cancerous and non-cancerous

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tissue and details of their sources are given in Table 1. Of the 3 human prostate cancer cell lines investigated, the LNCaP model is the only one which is hormonally responsive(Horosewicz *et al.*, 1983), whereas the other 2 cell lines, the DU145 (Stone *et al.*, 1978) and the 1013L (Williams, 1980) were all hormone-insensitive. All cell lines were maintained at 37°C under a humidified atmosphere at 5% CO_2 and 95% air in 75 cm^2 tissue culture flasks (Corning, New York, USA). The culture medium used was RPMI-1640 (Gibco, Paisley) supplemented with 10% (v/v) fetal calf serum, 20 mM HEPES, penicillin (100 units/ml), streptomycin (100 μg/ml) and 1% (v/v) L-glutamine. At each transplant, cells from the confluent monolayer were removed by trypsinisation (trypsin 0.05%, EDTA 0.025%, Gibco) and suspended at 5×10^4 cells/ml in the growth medium.

Growth assays

Dose-response curves of Cernitin T-60 treatment were determined using the following method. Triplicate determinations for each treatment were performed in 24 well culture plates (Cell-Cult, Sterilin, Teddington). Each well was seeded with 5×10^4 cells and incubated overnight in the medium under incubation conditions as described above for routine cell culture. The following day, the T-60 stock solution was serially diluted in supplemented RPMI 1640 medium to yield concentrations of 1–4 mg/ml. Controlled cultures receive medium alone. For the dose-response curve studies, the cells were exposed to cernitin T-60 for a total period of 4 days, with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 for 1, 2, 3 or 4 days. Experiments were terminated by the removal of cells from the monolayer by 2 successive trypsinisations and the pellets of harvested cells were subsequently suspended in 0.5 ml of Dulbecco A Medium (Oxoid Ltd, Basingstoke). The counting of cells was achieved on a haemocytometer slide after a 1–2 dilution with trypsin/glutamine.

Nuclear androgen receptors

Methods used for the preparation of nuclear fractions and measurements of androgen receptors followed those previously published (Habib *et al.*, 1986). For androgen receptor determinations, the competition binding assay was with 17α-methyl-^{3}H-methyltrienolone (R1881) in the presence of triamcinolone acetonide. Dissociation constants (Kd) and number of binding sites were determined by the Scatchard (1949) method.

Assay for 5α-reductase activity

5α-reductase was assayed at 37°C by following the conversion of (^{3}H) testosterone to (^{3}H) dihydrotestosterone and (^{3}H) 3α)β) androstanediol as previously detailed Habib *et al.*, 1985).

Results

The effect of T-60 on cell growth

Proliferation curves of the hormone-sensitive and hormone-insensitive prostate cell lines in the ab-

Table 1 Details of Cell Lines

Cell line	*Tumour type*	*Source*	*Cell/well*	*Duration of drug exposure (days)*
HEP	Cancer of the larynx	Gifts from Dr Mary Norval, University Medical School, Edinburgh	5×10^4	1–4
CHANG	Cancer of the liver		5×10^4	1–4
HEF	Human embryo fibroblast		5×10^4	1–4
RT112	Cancer of the bladder	Dr J. R. W. Masters, Department of Pathology, St Paul's Hospital, London	5×10^4	1–4
SUZA	Cancer of the testis		5×10^4	1–4
DU145	Cancer of the prostate	Gifts from Dr D. Mickey, Department of Urologic Research, University of North Carolina, USA	5×10^4	1–4
1013L	Cancer of the prostate		5×10^4	1–4
LNCaP	Cancer of the prostate	Gift from Dr J. S Horoszewicz, Department of Medical Virology and Oncology, Roswell Park Memorial Hospital, Buffalo, USA	5×10^4	1–4
MCF-7	Cancer of the breast	Gift from Dr W. R. Miller, Department of Clinical Surgery, University Medical School, Edinburgh	5×10^4	1–4

sence and presence of increasing concentrations of T-60 for periods of up to 4 days are shown in Figure 1. Although the growth of each of these prostate cell lines was slowed following the addition of the pollen extract, the results show that the inhibition was much more marked in the case of the androgen-insensitive cell lines. Indeed, at 1 mg/ml the pollen had no effect on the growth of the LNCaP cells, which exhibited an identical profile to that of the control, whereas the androgen-insensitive 1013L and DU145 cells demonstrated significant inhibition, particularly on day 4. By contrast, at the higher pollen concentrations (4 mg/ml) the growth of all 3 prostate cell lines was arrested and the cell numbers were rapidly depleted with the time of exposure. After 4 days, cell counts had been reduced by an average of 94% compared with controls.

Parallel experiments on the non-prostate derived cell lines showed no response to pollen extract (1 mg/ml) even after 4 days' exposure (Fig. 2). However, at the higher concentrations (4 mg/ml) the pollen induced some inhibition with the HEF and RT112 cells ($P<0.01$) following a 4-day incubation (Fig. 2), although this was not as marked as in the prostate cells. Significantly, none of the other non-prostate derived cells showed any significant response ($P>0.5$).

The effect of T-60 on androgen metabolism and steroid receptors

We also tested the impact of increasing concentrations of cernitin T-60 (0–10 mg/ml) on the 5α-reductase activity of tissue obtained from 6 separate BPH patients. As demonstrated in Table 2, there was no change in the activity of the enzyme with increase in T-60 even at concentrations as high as 10 mg/ml.

Table 2 Effect of T-60 Concentration on 5α-Reductase Activity of the Human Benign Prostate

Patient no.	*T-60 concentration (mg/ml)* 0	0.75	2	10
1	1.44±0.2*	1.34±0.23	1.38±0.12	1.25±0.09
2	1.55±0.18	2.08±1.10	0.98±0.12	1.58±0.29
3	6.29	6.98±2.72	8.46±1.29	9.89±0.89
4	2.21±0.15	2.18±0.19	—	2.23±0.23
5	2.98±0.52	3.18±0.21	4.45±0.56	—
6	2.58±0.26	2.4 ±0.24	2.32±0.04	2.28±0.65

* Values expressed in pmol/mg protein/min ± SD

Table 3 Effect of Cernitin T-60 (4 mg/ml) on Nuclear Androgen Receptor Measurements in 6 BPH Specimens

Treatment	K_d *(nmol/l ± SD)*	*Binding site (fmol/g tissue ± SD)*
Control	2.95±0.60	84.4±27.5
T-60 added	2.80±0.57	78.8±32.1

In addition, we undertook several experiments to measure nuclear androgen receptor levels in the absence and presence of the pollen extract at 4 mg/ml. The results summarised in Table 3 indicate that there was no significant difference between the control and test groups with regard to the number of binding sites ($P>0.5$) and dissociation constants ($p>0.5$).

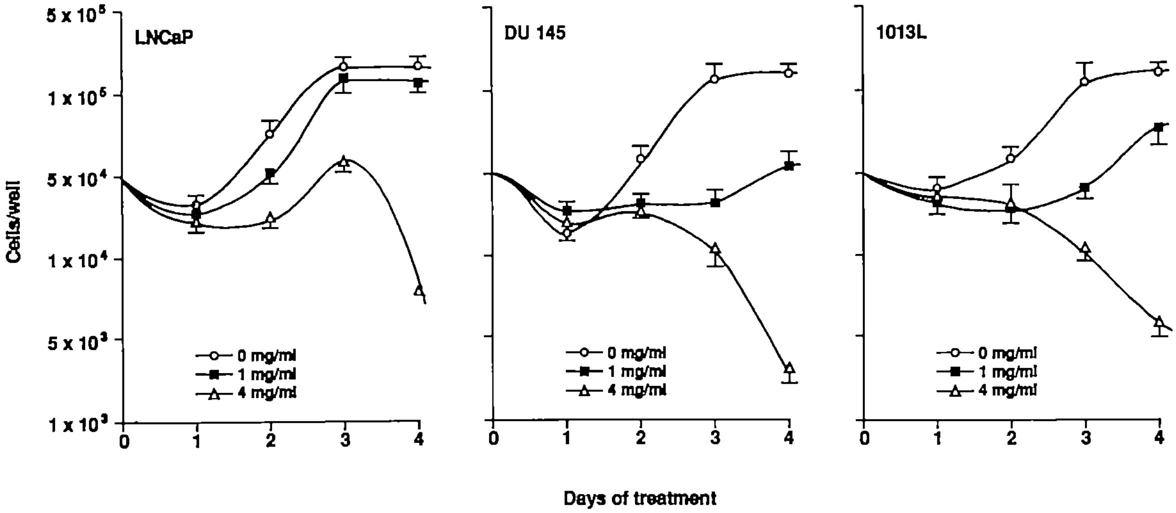

Fig. 1 The effects of varying the concentrations of Cernitin T-60 on the growth of androgen-sensitive and androgen-insensitive prostate cell lines. Each point represents the mean ± SD of 3 separate experiments each run 6 times

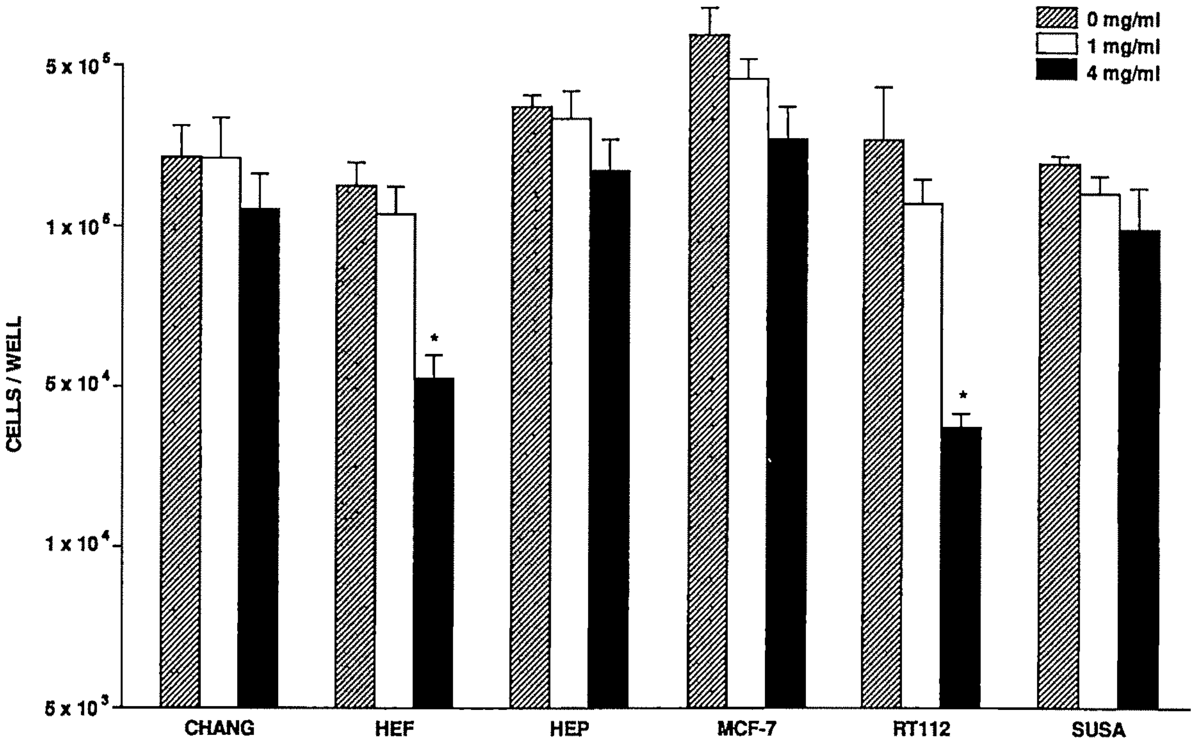

Fig. 2 The effect of Cernitin T-60 on the growth of 6 non-prostate derived cell lines after 4 days' exposure to the drug. Results are the mean ± SD of 3 separate experiments each run 6 times ($P<0{\cdot}01$)

Discussion

These data represent the first report on the *in vitro* evaluation of the water-soluble fraction of the pollen extract, Cernitin T-60, using a panel of human prostate tumour-derived continuous cell lines. In addition, parallel *in vitro* experiments were also undertaken on 6 other cell lines derived from non-prostatic sources essentially to assess the specificity and efficacy of the pollen extract.

Attempts to minimise variations between experiments were made by standardising experimental conditions with regard to the same medium, fetal calf serum concentration, and narrow range of cell passages. Furthermore, we observed a little variation in drug response with repeated experiments for each particular cell line. Nonetheless, the results of this study suggest that the responses induced were varied and these were predominantly a function of the cell lines: high in the case of the prostate, low or non-existent in the non-prostate derived cells. Of interest also is the heterogeneity in responses of the prostate cell lines to the agent. The hormone-insensitive cells demonstrated a greater sensitivity to the pollen extract than the androgen-dependent line and this was particularly evident at the lower pollen concentrations.

We are not yet sure of the mechanism of action of this drug but quite obviously it is not mediated via the androgen delivery system of the cell, since the pollen had no effect on either the 5α-reductase activity of the tissues or its steroid receptors. There have also been reports suggesting that Cernilton might be a potent inhibitor of the cyclo-oxygenase and lipoxygenase enzymes which are needed for leucotrine and prostaglandin synthesis (Loschen, personal communication) but these reports have not been extended to the prostate and will require verification.

However, it is gratifying to note that the selectivity of the pollen extract for the prostate, as demonstrated in the present study, was also supported by the work carried out by Ito *et al.* (1986). Following an intake of Cernilton over a period of 21 days, the rats in the latter study showed significant reductions in the weight of the ventral and dorsal prostate but there was no change in any of the other major organs. Following these encouraging results, a double-blind trial was undertaken on a group of patients with BPH, the results of which are described by Buck *et al.* (1990).

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The Authors

F. K. Habib, PhD, CChem, FRSC, Senior Lecturer in Biochemistry, University Department of Surgery, Western General Hospital, Edinburgh.

Margaret Ross, BSc, Research Technician, University Department of Surgery, Western General Hospital, Edinburgh.

A. C Buck, PhD, FRCS, Consultant Urologist, Royal Infirmary, Glasgow.

L Ebeling, MD, Medical Associate, Hamburg, Germany

A. Lewenstein, PhD, General Manager, Cernitin S.A , Lugano, Switzerland.

Requests for reprints to F. K. Habib, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

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Treatment of Outflow Tract Obstruction due to Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton

A Double-blind, Placebo-controlled Study

A. C. BUCK, R. COX, R. W. M. REES, L. EBELING and A. JOHN

Department of Urology, University Hospital of Wales, Cardiff

Summary—Whilst prostatectomy remains the "gold standard" for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment—if only for symptomatic relief—appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or the sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo-controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69% of the patients) compared with placebo (30%). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A–P) diameter of the prostate on ultrasound. However, differences in respect of flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect in BPH and may have a place in the treatment of patients with mild or moderate symptoms of outflow obstruction.

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; Habib *et al.*, 1981; Stone *et al.*, 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological.

More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symptoms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of "prostatism", interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade (Lancet, 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH (Takeuchi *et al.*, 1981; Becker and Ebeling, 1988) prompted us to carry out a placebo-controlled, double-blind study to evaluate its effect in patients with outflow obstruction due to BPH.

Patients and Methods

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean 68.6 ± SD 7.7). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules *bd* over a 6-month period.

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The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes <150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete empyting, terminal dribbling and dysuria, with a score of 0–3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) (Boyarsky *et al.*, 1977).

In addition, a full haematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipoproteins. All blood samples were obtained between 09.00 and 10.00 h, following an overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

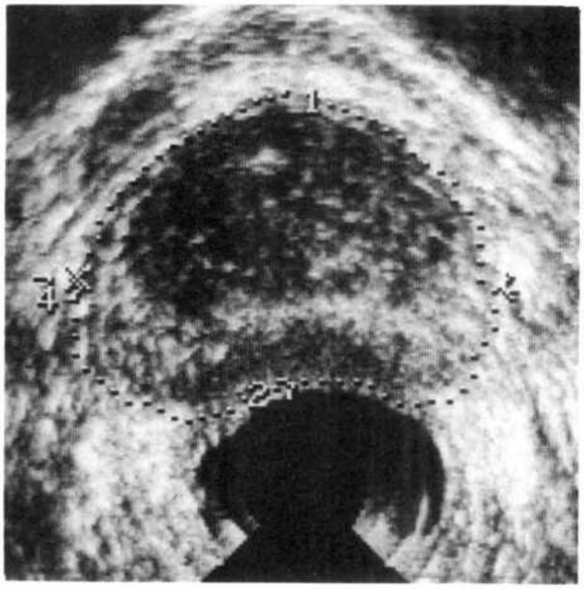

Fig. 1 Frame showing the prostate in its largest dimension.

Statistical method and analysis

The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of χ^2 tests for categorical data, χ^2 test with Yates' correction (4-fold tables) and Student's t test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the χ^2 test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anaemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight ($P = 0.05$).

Subjective evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups ($P = 0.66$), but 60% of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30% of patients on placebo ($P < 0.063$). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10% in the placebo group ($P < 0.004$). There were no significant differences in hesitancy ($P = 0.48$), urgency ($P = 0.157$), intermittency ($P = 0.5$), terminal dribbling ($P = 0.9$) or dysuria ($P = 1.0$). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group (69% of patients) compared with patients in the placebo group (29%) ($P < 0.009$) (Table 1).

Table 1 Frequency of Symptom-free Findings following Cernilton and Placebo at 6 Months

	Response Rate (%)		
Symptom	*Cernilton*	*Placebo*	*P value*
Frequency			
Daytime	37	47	0.664
Nocturia	60	30.4	0.063*
Hesitancy	47	29	0 480
Urgency	71	45	0.157
Intermittency	52	33	0 505
Incomplete emptying	57	10	0 004*
Terminal dribble	61	56	0.99
Dysuria	62	71	1.0

* Statistically significant.
Some test results remained non-significant because of the small number of positive findings before the start of treatment.

Objective evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume (slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving Cernilton compared with the placebo group, in whom it increased ($P < 0.025$) (Fig. 2).

The results of ultrasound measurement of the parameters for prostate volume are shown in Table 3. The A–P diameter was found to be significantly reduced after treatment with Cernilton at 6 months ($P < 0.025$) (Fig. 3).

There were no significant changes in the haematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term, whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms or retention (Fowler *et al.*,

Table 2 Results of Measurements before and after Treatment

		Cernilton		*Placebo*		*Analysis of variance*
Parameter	*Time of examination*	$\bar{X}$	*SE*	$\bar{X}$	*SE*	*(P value)*
Peak flow rate (ml/s)		(n=26)		(n=24)		
	Before treatment	10.3	5 2	11.8	6.4	0.92
	After treatment	10.5	5.1	12.1	5 1	
Volume voided (ml)		(n=29)		(n=24)		
	Before treatment	241.5	144	235	96 8	0.11
	After treatment	203.4	90.3	257	106.6	
Residual urine (ml)		(n=28)		(n=24)		
	Before treatment	145.4	107.5	93.4	91.4	0.025*
	After treatment	101.9	87.3	113.4	87.3	

* Statistically significant.

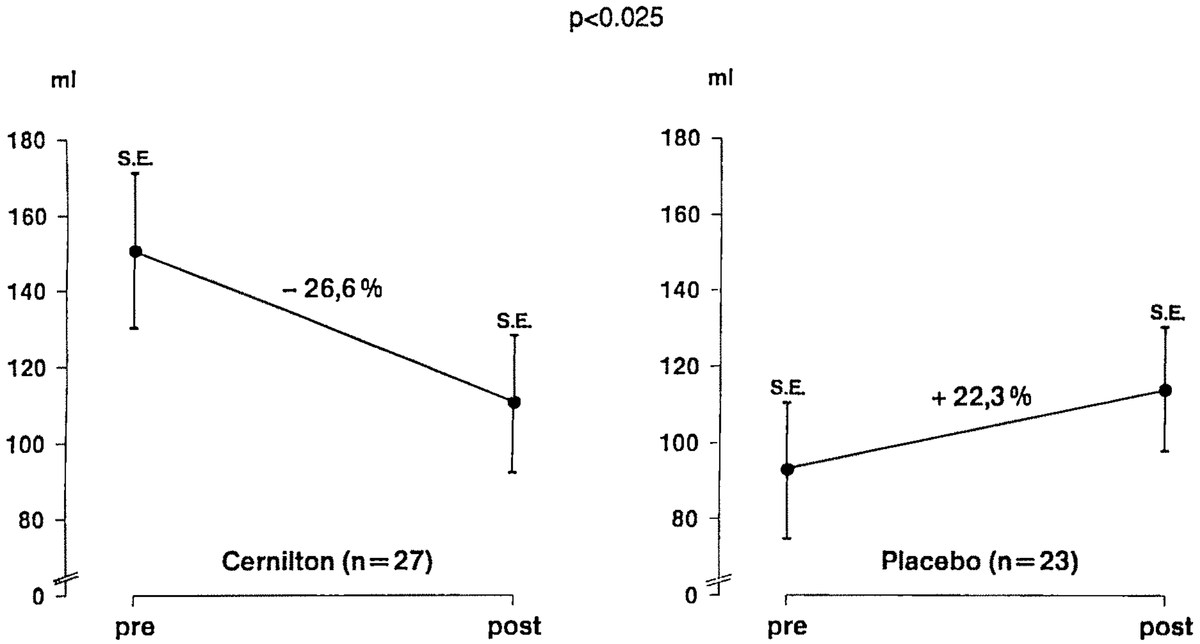

Fig. 2 Residual urine volume

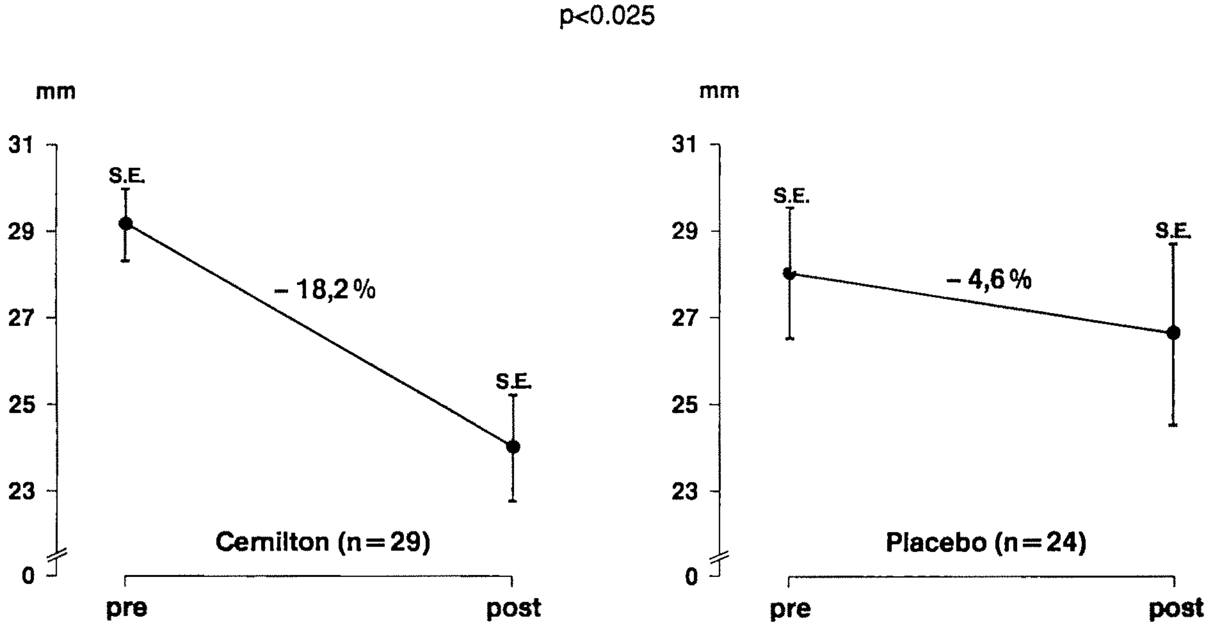

Fig. 3 Prostate volume

1988). Thus there may be a place for therapeutic compounds that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery.

Several studies aimed at achieving androgen deprivation in BPH have been reported. These have included castration (Huggins and Stevens, 1940), oestrogens (Beacock *et al.*, 1985), progestogens (Geller *et al.*, 1965; Hald and From, 1972), anti-androgens (Caine *et al.*, 1975) and, more recently, LH-RH agonists (Gabrilove *et al.*, 1987; Peters and Walsh, 1987). With the introduction of selective α1 adrenergic blockers there has been renewed interest in their use for symptomatic relief (Caine, 1986; Kirby *et al.*, 1987). The discovery of

Table 3 Measurement of Prostate Volume

Prostate size	*Time of examination*	*Cernilton* $\bar{X}$	*Cernilton* *SE*	*Placebo* $\bar{X}$	*Placebo* *SE*	*Analysis of variance (P value)*
Circumference (mm)		(n = 29)		(n = 17)		
	Before treatment	169.6	26.3	163.2	16.2	0.446
	After treatment	153.4	27.5	150.5	21.6	
Transverse diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	56.4	8.3	53.8	8.1	0.753
	After treatment	52.2	9.7	50.3	8.1	
Anteroposterior diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	29.1	5.3	28.3	7.4	0.025*
	After treatment	23.8	7.0	26.7	9.1	

* Statistically significant.

high concentrations of cholesterol in BPH has led to the use of cholesterol-lowering drugs such as candicidin, with variable results (Jensen and Madsen, 1983). However, none of these compounds has proved to be consistently effective and most have significant untoward side effects.

An interesting empirical approach to the non-adrenergic, non-hormonal treatment of symptomatic BPH has been the use of pharmacological compounds derived from plants. Donkervoort *et al.* (1977) evaluated Tandenan, an extract of African prunes, in a double-blind study in 20 patients. Although the drug was harmless, it had no beneficial effect. An extract from the fruit of the American dwarf palm, Serenoa repens, reputed to have anti-androgenic activity, brought about a significant improvement in flow rate, residual urine and nocturia, although peak urine flow rates did not reach normal values in the large group of patients studied (5.35 ± SE 1.51 before and 8.05 ± SE 2.47 after treatment; n = 46) (Champault *et al.*, 1984).

The pollen extract, Cernilton, known to be effective in the treatment of chronic abacterial prostatitis and prostatodynia (Ohkoshi *et al.*, 1967; Ebeling, 1986; Buck *et al.*, 1989), has also been shown to provide symptomatic relief in patients with benign prostatic hyperplasia (Takeuchi *et al.*, 1981; Becker and Ebeling, 1988). Cernilton is an extract of pollen derived from several different plants in southern Sweden. It is rendered free of allergens and its 2 principal active constituents are a water soluble fraction, T-60, and an acetone soluble fraction, GBX. The acetone-soluble fraction was found to consist of 3 β-sterols with a similarity on UV absorption spectra to oestrone and Stigmasterol (Kvanta, 1968). Cernilton produced a significant decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals (Ito *et al.*, 1986). Habib *et al.* (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice was significantly inhibited by Cernilton extract, but no histological differences were observed between the treated and untreated groups (Otto *et al.*, 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo-controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) (Ockerman, personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Kimura *et al.* (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase *et al.* (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cernilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind, placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronise the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

Acknowledgements

We thank Mr Golding of Kretztechnik (UK) for his generous help in supplying the ultrasound equipment Our thanks are also due to Dr J. Schnitker and Dr H.-F Koch, of the Institut für Angwandte Statistik Dr Jorg Schnitker Gmbh, for statistical analysis of this work

Appendix

Daytime Frequency

0–1 to 4 times daily
1–5 to 7 times daily
2–8 to 12 times daily
3–13 or > times daily

Nocturia

0—absence of symptoms
1—subject awakened once each night because of the need to urinate
2—subject awakened 2 to 3 times each night
3—subject awakened 4 or > times each night

Hesitancy

0—occasional hesitancy (occurs in 20% or fewer of subject's attempts to void)
1—moderate hesitancy (occurs during 20 to 50% of subject's attempts to void)
2—frequent hesitancy (occurs more than 50% of subject's attempts to void)
3—symptoms always present, lasts for 1 minute or longer

Urgency

0—absence of symptoms
1—occasionally difficult for subject to postpone urination
2—frequently difficult (more than 50% of the time) to postpone urination and may rarely loose urine
3—always difficult to postpone urination and subject sometimes loses urine.

Intermittency

0—occasional intermittency (occurs in 20% or fewer of subject's attempts to void)
1—moderate intermittency (occurs during 20 to 50% of subject's attempts to void)
2—frequent intermittency (occurs more than 50% of the time, but not always, and may last up to 1 minute)
3—symptoms always present, lasts for 1 minute or longer

Incomplete Emptying

0—absence of symptoms
1—occasional sensation of incomplete emptying of bladder after voiding
2—frequent (more than 50% of the time) sensation of incomplete voiding
3—constant and urgent sensation and no relief upon voiding

Terminal Dribbling

0—occasional terminal dribble (occurs in 20% or less of the subject's attempts at voiding)
1—moderate terminal dribble (occurs in 20 to 50% of subject's voiding)
2—frequent terminal dribble (occurs in more than 50% of the time but not always)
3—symptom always present, dribbling lasts for 1 minute or more, or wets clothes

Dysuria

0—absence of symptoms
1—occasional burning sensation during urination

2—frequent (more than 50 per cent of the time) burning sensation during urination
3—frequent and painful burning sensation during urination

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The Authors

A. C Buck, PhD, FRCS, Consultant Urologist, Royal Infirmary, Glasgow

R Cox, MD, FRCS, formerly Senior Registrar in Urology, University Hospital of Wales in Cardiff Now Consultant Urologist, Truro General Hospital, Truro.

R. W. M. Rees, FRCS, Consultant Urologist, University Hospital of Wales, Cardiff.

L. Ebeling, MD, Medical Associate, Hamburg, Germany.

A John, SRN, Research Sister, Department of Urology, University Hospital of Wales, Cardiff.

Requests for reprints to. A. C. Buck, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.

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Prostatic Carcinoma: Histological and Immunohistological Factors Affecting Prognosis

R. J. COHEN, G. GLEZERSON, ZENOBIA HAFFEJEE and D. AFRIKA

Department of Anatomical Pathology, South African Institute for Medical Research, Johannesburg, South Africa

Summary—Neuro-endocrine or paracrine cells of the human prostate and urethra have been identified by various methods, predominantly silver stains and immunocytochemistry. The incidence of neuro-endocrine differentiation in prostatic carcinoma has varied considerably from 10 to 100%, but has not been studied previously as an independent factor affecting prognosis.

Nucleolar organiser regions (NORs) are loops of ribosomal RNA occurring in the nucleoli of cells which ultimately process RNA genes. NORs have been demonstrated by silver (Ag) staining techniques and have been studied in numerous malignant tumours. A pilot study from this laboratory has shown a distinct and significant difference in AgNOR staining between prostatic carcinoma and benign prostatic epithelial hyperplasia.

A retrospective study was performed with at least 6 years' follow-up. This confirmed the presence of neuro-endocrine cells in more than half of the patients under investigation. A significant correlation between survival and the absence of neuro-endocrine cells was demonstrated. AgNOR staining was shown to be of no prognostic value.

The incidence of prostatic carcinoma in most western societies is second only to that of lung cancer, yet cancer of the prostate ranks only third as a cause of cancer deaths. This disparity between the incidence and mortality is an indication of this tumour's wide range of biological activity. Some patients with prostatic cancer progress rapidly and die within several months, while others have a much slower progression and ultimately die of unrelated causes.

Many studies have attempted to identify histologically and to sub-categorise those cases of prostatic carcinoma in which the prognosis is poor, so that the patient may be treated accordingly. In a large study (Gleason, 1977) it was convincingly demonstrated that those tumours which were poorly differentiated and had an anaplastic growth pattern had a significantly worse prognosis than tumours which were well differentiated and closely resembled normal prostatic acinar structures. The vast majority of tumours in that study (2585/2911) were graded "major pattern" II, III and IV, *i.e.* intermediate grade with an intermediate or unpredictable outcome. Therefore those patients who fell into groups I (histologically well differentiated carcinoma) and V (anaplastic carcinoma), in which the prognosis could be reliably predicted, represented only a small minority.

Endocrine or paracrine cells of the human prostate and urethra have been identified by various methods, predominantly silver stains and immunocytochemistry (Di Sant'Agnese and de Messy Jensen, 1987; Di Sant'Agnese, 1988). The incidence of neuro-endocrine differentiation in prostatic carcinoma has steadily increased as a result of increasingly sensitive methods of detection. Original reports (Azzopardi and Evans, 1971) showed that 10% of prostatic carcinomas contained argentaffin cells. In later studies, Kazzaz (1974) found argyrophilic cells in 16% of prostatic carcinomas and Capella *et al.* (1981) in 32.5% of these tumours. More recent reports (Di Sant'Agnese and de Messy Jensen, 1987) indicated that 47% of 53 cases of prostatic cancer exhibited neuro-endocrine differ-

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entiation. Abrahamson *et al.* (1986), using silver stains as well as multiple immunohistochemical markers, demonstrated an incidence of up to 100% in a small number of cases. A recent study (Tetu *et al.*, 1987) confirmed the aggressive nature of small cell carcinoma of the prostate and it was shown that poorly differentiated tumours were often associated with neuro-endocrine differentiation (Dauge and Delmas, 1987).

Nucleolar organiser regions are loops of ribosomal RNA occurring in the nucleoli of cells which ultimately process RNA genes. NORs have been demonstrated by silver staining techniques (AgNOR) and have been studied in numerous malignant tumours, namely malignant lymphoma (Crocker and Paramjit, 1987), cutaneous melanocytic lesions (Crocker and Skilbeck, 1987) and a small series of prostatic tumours (Ploten *et al.*, 1986). A pilot study in this laboratory (unpublished material) has shown a distinct and significant difference in AgNOR staining between prostatic carcinoma and benign prostatic epithelial hyperplasia.

The aim of this study was to correlate the prognosis of prostatic carcinoma with nucleolar organiser region staining and the presence of neuro-endocrine cells, independent of the tumour grade or stage. Whereas malignant tumours with predominant neuro-endocrine differentiation (carcinoid, small cell neuro-endocrine carcinoma) are biologically different from conventional carcinomas (Dauge and Delmas, 1987), it is generally thought that conventional carcinomas with focal neuro-endocrine differentiation are not substantially different from those not showing such differentiation (Lloyd *et al.*, 1984; Turbat-Herrera *et al.*, 1986).

Patients and Methods

Fifty-two patients were selected sequentially from the hospital records at this institution from October 1981 to June 1983. The records indicated that all of these patients were subjected to prostatic biopsy because of symptoms related to the local complications of the tumour. In all cases the pre-operative diagnosis was carcinoma stage B, C or D (13). Twenty-one patients were immediately excluded from the trial for the following reasons:

(i) Eight had died within 1 month of surgery. These deaths were attributed either to pulmonary thrombo-embolic disease or to medical complications unrelated to the surgical procedure.
(ii) Five were excluded because no follow-up history was available.
(iii) In 5 cases no tissue was available for examination.
(iv) In 3 cases the original diagnosis was incorrect (transitional cell carcinoma).

The remaining 31 patients were followed up to the time of writing or to date of death. In each case the cause of death had been documented and, where available, post mortem tissue or further surgical specimens were examined. Three patients had died 4, 6 and 6.5 years after the original diagnosis. Post mortem material showed that each had died of unrelated causes and there was no post-mortem evidence of residual prostatic carcinoma. These 3 patients were thus included in the surviving group.

The specimens had been fixed in 10% phosphate buffered formalin and processed to wax paraffin. Four 2-μm sections were cut and taken to aqueous solution through graded alcohols. One section was submitted to the AgNOR staining procedure at room temperature for 50 min (Ploten *et al.*, 1986). Two sections were submitted to immunoperoxidase staining, namely polyclonal, neuron-specific-enolase (NSE) (DAKO) and monoclonal Chromagranin A (ChA) (ENZO). Both of these peroxidase stains represent markers of neuro-endocrine cells (Lloyd *et al.*, 1984; Turbat-Herrera *et al.*, 1986). NSE represents a highly sensitive marker of neuro-endocrine cells, while Chromagranin A, although less sensitive, appears more specific (Abrahamson *et al.*, 1986).

AgNOR technique

The specimens were studied microscopically at a magnification of 1000 × ; 100 nuclei were examined using a simple eye-piece graticule to prevent recounting. The number of AgNORs were documented in the lining epithelial cells, disregarding stromal cells, inflammatory cells and blood vessels. This assessment was conducted without prior knowledge of the patient's history (Fig. 1).

Immunoperoxidase technique

Sections stained for ChA and NSE were examined by an independent observer and the staining was recorded as negative (no neuro-endocrine cells seen) or positive (individual cells or groups of cells showing positive staining) (Fig. 2). In 3 cases non-specific staining was noted; this was assessed by a second independent pathologist and recorded as negative.

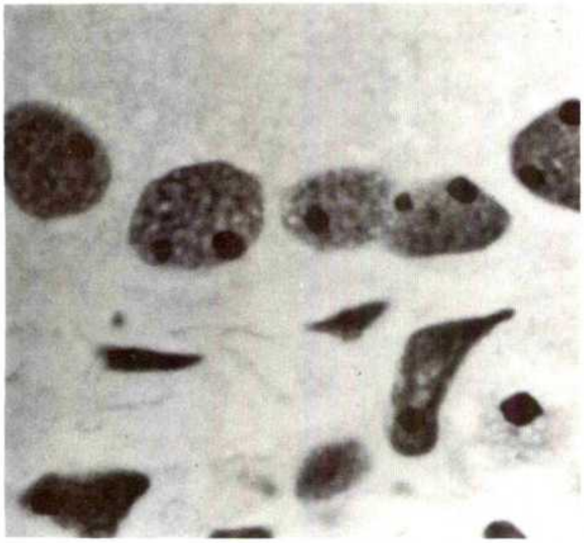

Fig. 1 AgNOR precipitation noted in prostatic carcinoma. The precipitates appear as irregular and multiple intranuclear black dots. (×990).

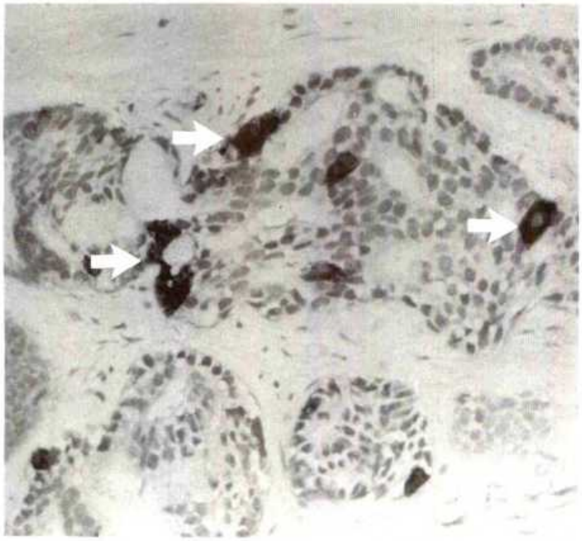

Fig. 2 Immunoperoxidase staining for Chromagranin A (ENZO) shows the presence of neuro-endocrine cells scattered in an otherwise well to moderately well differentiated carcinoma. (×200).
(The identical picture is seen in stains for neuron specific enolase).

Results

At the time of follow-up (1989), 11 patients (36%) were alive and well with no clinical evidence of disease; all were shown to be negative for NSE and ChA. The 3 patients who died of unrelated disease were also negative for NSE and ChA immunoperoxidase staining. Of the 17 patients who died of prostatic cancer, 15 were positive for NSE and 14 for ChA; 2 of the 17 were negative for both peroxidase stains.

Survival graphs were plotted, comparing patients with positive staining tumours to those with negative results. Figure 3 represents the total population survival over 7 years. Figure 4 compares tumours positive for NSE with those negative for the stain. Figure 5 compares survival of patients positive for ChA with those negative for ChA staining. It should be noted that the very significant but less striking survival curve noted for ChA may be related to its lower sensitivity compared with NSE. Figure 6 illustrates the striking association between survival and tumours negative for neuro-endocrine markers ($P<0.001$). The intensity of the staining for NSE and ChA did not appear to be related to outcome.

AgNOR counts performed had a mean count of 579.5/100 nuclei in the patients dying of prostatic cancer (SD 157.5). The mean AgNOR count in the surviving patients was 487.8 (SD 116.7). Using the pooled data formulae (t test), a t value of 1.69 was obtained, indicating no significant difference at $P=0.05$. This indicates that although AgNOR staining may be useful in distinguishing prostatic carcinoma from benign prostatic epithelium, it appears to have no value as a prognostic indicator.

Discussion

The occurrence of neuro-endocrine cells in prostatic carcinoma is variable, depending on the method used to demonstrate these cells. In the present study, approximately 60% of tumours showed neuro-endocrine differentiation; none histologically resembled a carcinoid tumour or small cell carcinoma. The aggressive behaviour of these tumours is noted from the above statistics and is, therefore, of both therapeutic and diagnostic importance. It has been suggested that chemotherapy, similar to that used for small cell carcinoma of the lung (Turbat-Herrera *et al.*, 1986) be used for small cell carcinoma of the prostate. The influence of this new prognostic marker on the interpretation of the results of treatment and the selection of treatment needs to be investigated. We believe that this could best be done by a multi-centre co-operative study group that could rapidly provide a large data base from which to work.

Finally, we propose that although the presence of neuro-endocrine cells in other tumours (Smith

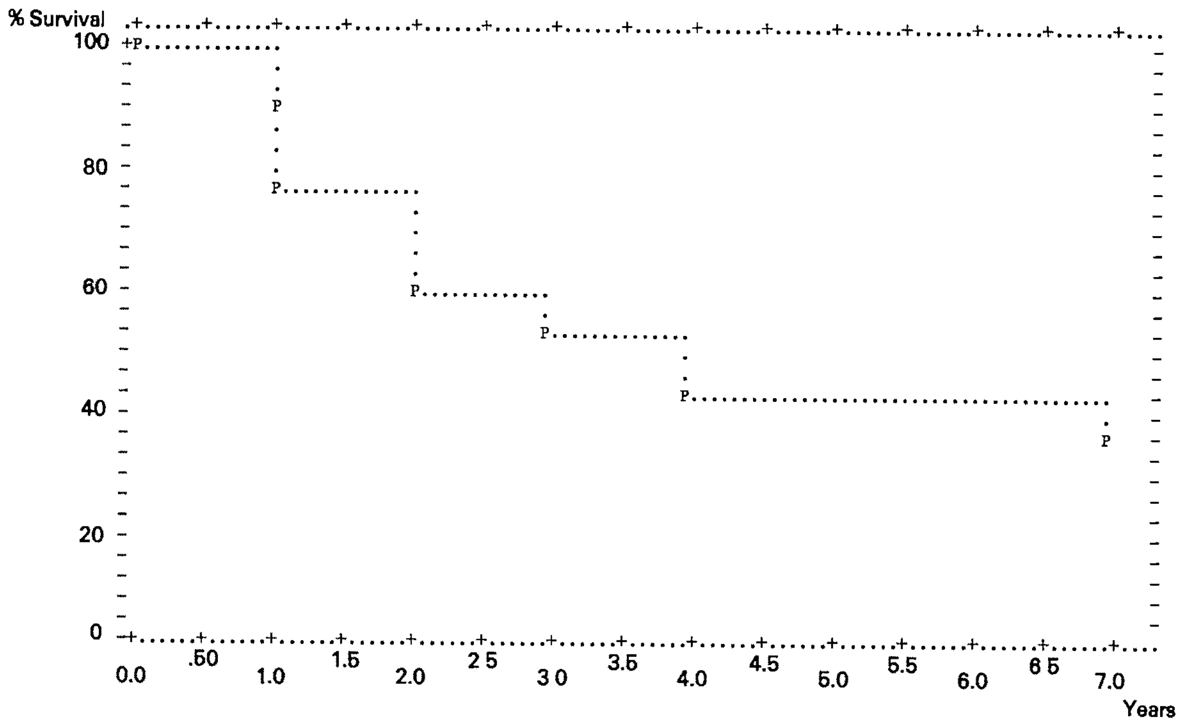

Fig. 3 Survival of total population.

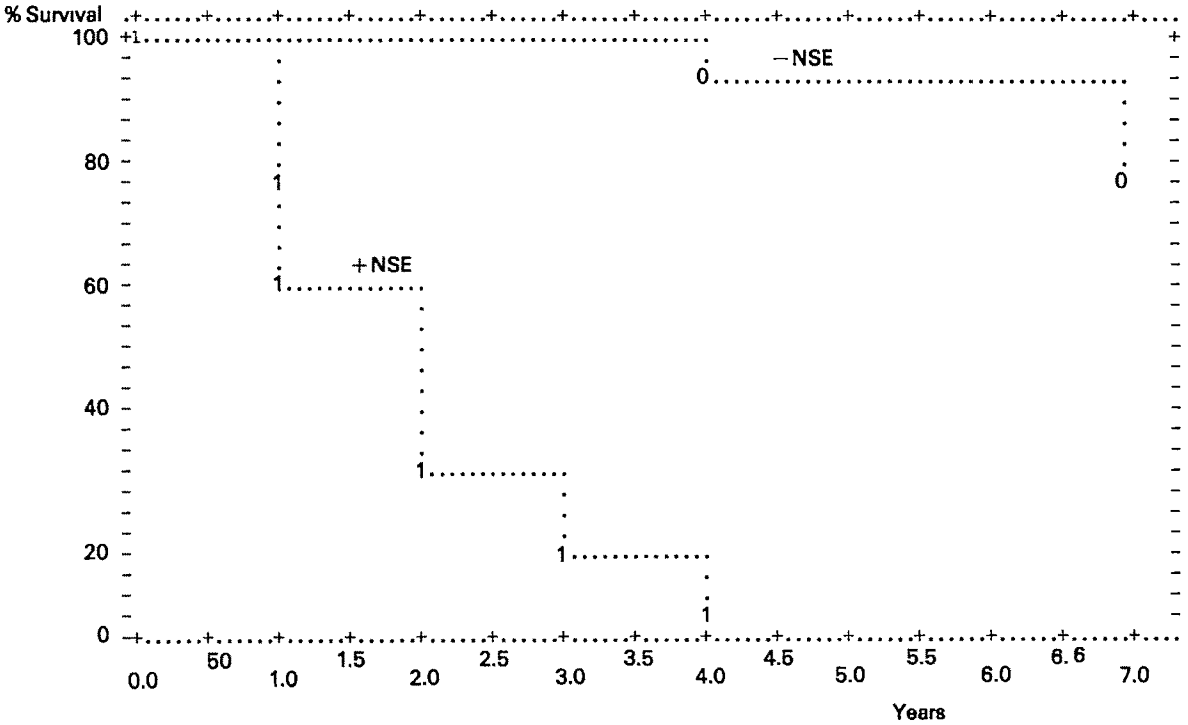

Fig. 4 Comparison of tumours positive for NSE with those that were negative for NSE. Generalised Wilcoxon—$P<0.0001$. Generalised Savage—$P<0.001$.

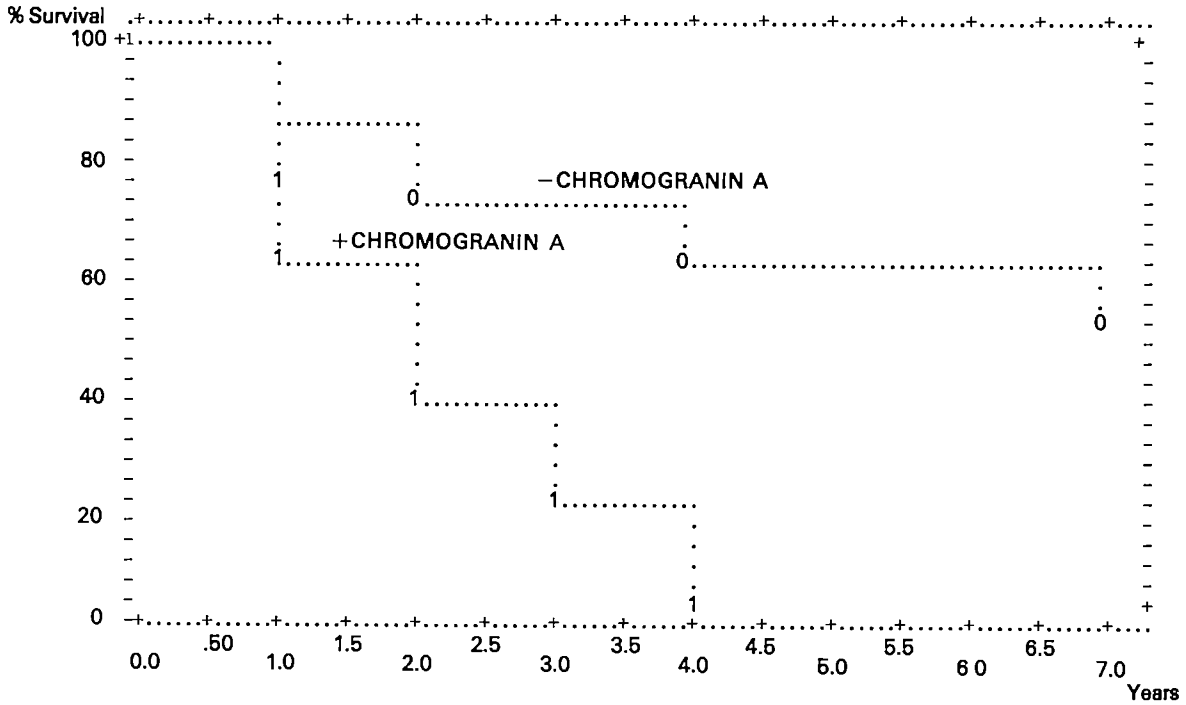

Fig. 5 Survival of patients positive for ChA with those who were negative for ChA. Generalised Wilcoxon—$P<0.0001$. Generalised Savage—$P<0.001$.

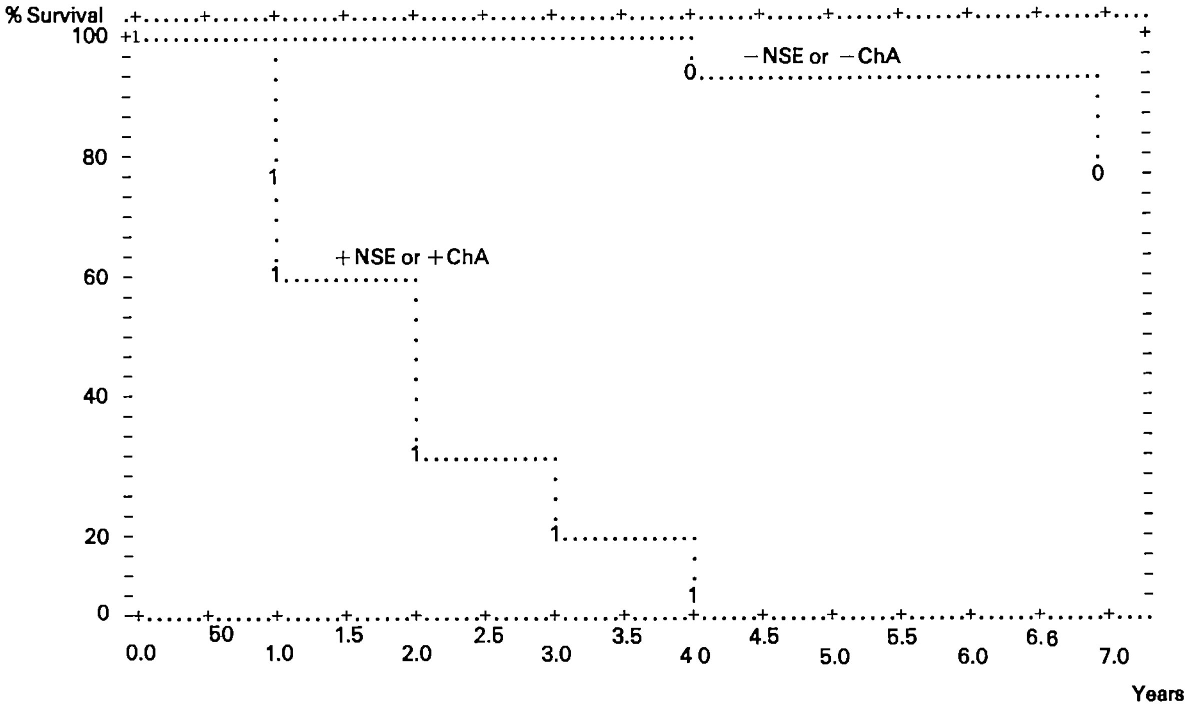

Fig. 6 Association between survival and tumours negative for neuro-endocrine markers. Generalised Wilcoxon—$P<0.0001$. Generalised Savage—$P<0.001$

and Haggitt, 1984; Bonar and Sweeney, 1986) may be of no prognostic importance, it is of prognostic significance in prostatic adenocarcinoma. An additional factor to emerge from the study was the finding that AgNOR staining appears to have no prognostic implications in prostatic carcinoma.

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The Authors

R. J. Cohen, FFPath(SA), Consultant Pathologist, Johannesburg Hospital Laboratory.

G Glezerson, MBBCh (Witwatersrand), Registrar, Department of Urology, University of the Witwatersrand

Zenobia Haffejee, National Diploma in Medical Technology (Witwatersrand), Medical Technologist, Johannesburg Hospital Laboratory.

D. Afrika, National Diploma in Medical Technology (Witwatersrand), Medical Technologist, South African Institute for Medical Research

Requests for reprints to: R. J. Cohen, Department of Anatomical Pathology, South African Institute for Medical Research, P.O. Box 1038, Hospital Street, Johannesburg 2000, South Africa.

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Distribution of Bony Metastases in Prostatic Carcinoma

J. CUMMING, N. HACKING, J. FAIRHURST, D. ACKERY and J. D. JENKINS

Departments of Urology and Nuclear Medicine, Southampton University Hospitals, Southampton

Summary—Fifty-five prostate cancer and 55 breast cancer patients with positive bone scintigrams were studied. The pattern of spread in the axial skeleton and pelvis showed differences between the 2 groups. This difference was not related primarily to bone volume at the site of metastasis. The difference in distribution of bony metastases between breast and prostate is explained by our knowledge of Batson's vertebral venous plexus.

Knowledge of the existence of the vertebral venous system dates back to Vesalius but our modern concepts of this system and its importance have been attributed to Batson (1940). He injected the cadaveric dorsal vein of the penis with radio-opaque material and showed the connection with the prostatic plexus and subsequently the pelvic veins, pelvic bones and sacral canal. This, he felt, replicated the spread of prostatic metastases and was evidence for the vertebral venous system being the channel through which the malignant cells passed to their implantation in the bones.

This has not received uniform acceptance. Animal experiments (Zeidman and Buss, 1952) have shown that tumour cells can pass through the pulmonary vessels and into the pulmonary circulation. Franks (1956) felt that early spread of prostatic cancer was probably through the vertebral venous system but that later the systemic circulation was involved. Willis (1973) was of the opinion that the cancer spread to the pulmonary circulation initially and from this site "tertiaries" metastasised to bone, etc.

Dodds *et al.* (1981), in a review of positive bone scintigrams from different cancers, found little difference in overall distribution between the various cancers. They concluded that the systemic circulation was of primary importance in conveying the malignant cells to their site of metastasis. Prostate and breast cancers were included in their study, having primary sites in different parts of the body and yet a very similar, widely distributed pattern of bony secondaries.

We employed prostate and breast cancer as a model to study the pattern of bony metastases from these 2 sites.

Methods

A review of all positive bone scintigrams in 1988 from carcinoma of the prostate revealed 55 records. This was matched with the first 55 positive bone scintigrams in carcinoma of the breast in 1988.

Each metastasis affecting the axial skeleton and pelvis was separately recorded on a graphic outline of the skeleton; 25 patients had more than 1 scintigram and these were detailed in different colours to show the pattern of spread of the disease.

The possibility of frequency and amount of metastases being related to the amount of bone at the site of metastasis was explored by comparison of the sites of metastases with the volume of bone. Vertebral volumes were measured by fluid displacement technique in skeletons from each sex. The sacrum and hemipelvis were also included. Adjacent vertebrae were paired so that the results could be graphically presented; the sacral and hemipelvic volumes were counted on their own. A reference to bone volumes could not be found—hence the rather simple method employed.

Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Results

The distribution of bony metastases is shown in Figure 1. The whole spine may be involved in both prostatic and breast carcinoma but almost twice the number of metastases were found in positive bone scintigrams of prostatic cancer compared with breast cancer. In addition, the sacrum and pelvis were much more heavily involved in prostatic carcinoma.

In patients with prostatic carcinoma the spine was almost always involved when the bone scintigram was positive (53/55). Figure 2 shows the sites along the axial skeleton and pelvis which were free from metastases. The sacrum, pelvis and lumbar spine were spared in only 2/55 patients (4%). By contrast, 13/55 (24%) were spared in breast carcinoma.

Figures 3 and 4 compare the site of metastasis with vertebral volume in prostate and breast cancer respectively. The bone volumes become steadily greater the further one progresses inferiorly and the sacral spine and hemipelvis are correspondingly large, especially in the female skeleton. However, the distribution of breast carcinoma secondaries bears little relation to bone volume; otherwise more involvement of the sacrum, lumbar spine and pelvis would be evident. In the prostatic cancer patients, the number of metastases is greater in the lower skeleton than in the upper, but on closer inspection this is not primarily related to bone volume. In the thoracic spine the proportion of metastases to volume is much greater than in the lower spine and pelvis.

There were 25 patients who had more than 1 scintigram and the results are shown in the Table. This shows that progression of metastatic disease appears to involve further extension of the initial secondaries in some cases and new secondaries in others.

Table Results of Scintigrams

	No. of patients
First normal, second positive	5
No change or improved	3
Local extension only	1
< 5 new metastases	2
> 5 new metastases	11
Superscan becoming more diffuse	3
Total	25

Discussion

The vertebral venous system lies outside the thoraco-abdominal cavity and involves the cerebral

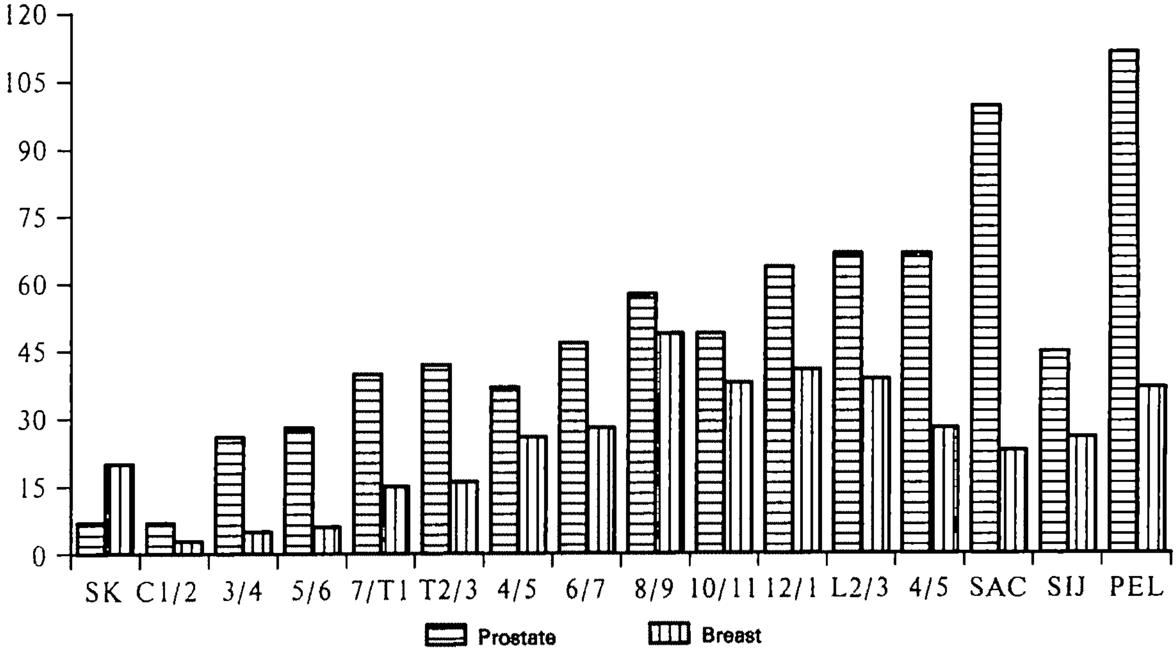

Fig. 1 The site of each metastasis from each bone scintigram has been recorded. The figure shows the total number of metastases at each site along the axial skeleton for cancer of the prostate and the breast.

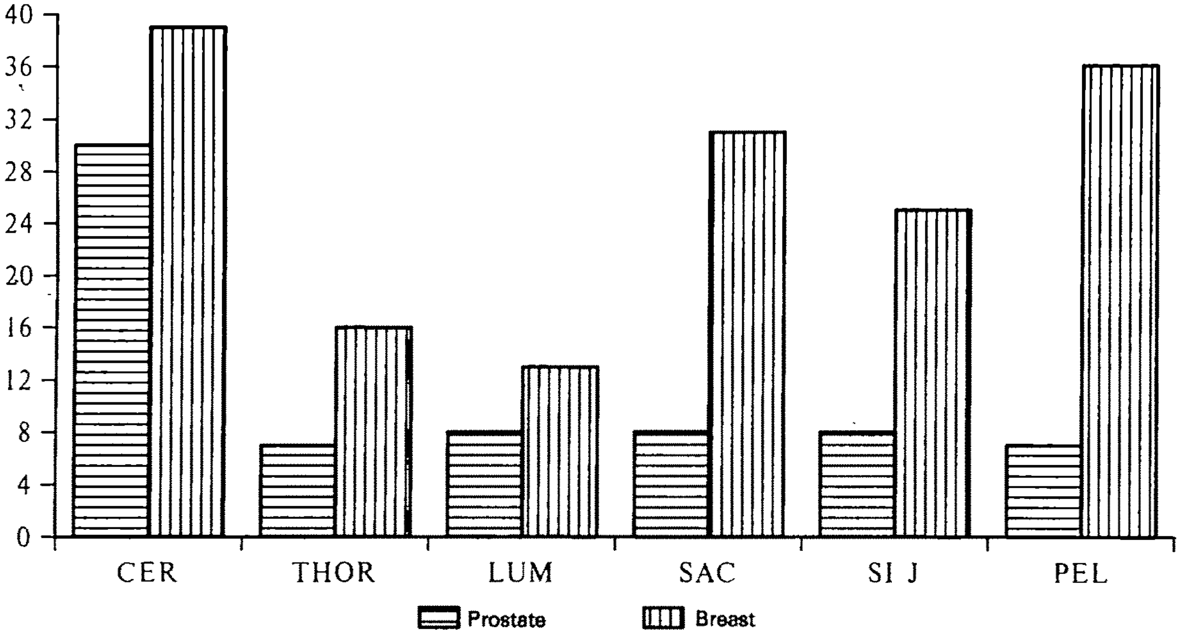

Fig. 2 Those sections of the axial skeleton that were free from metastases are illustrated. Few spines from the prostate cancer group were spared, but it was not uncommon for major sections of the spine to be free from metastases, especially the sacrum and pelvis, in the breast cancer group.

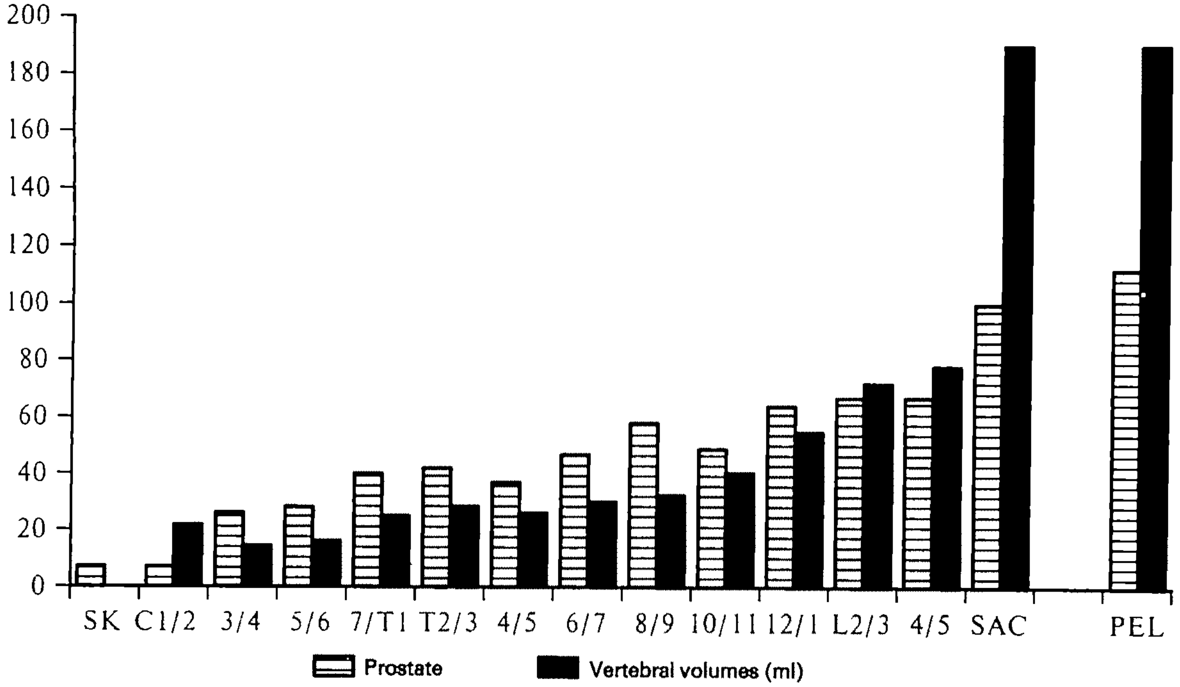

Fig. 3 The number of metastases from carcinoma of the prostate in the vertebrae has been compared with the volume of the vertebrae. This shows that the number of metastases is not related primarily to the amount of bone present.

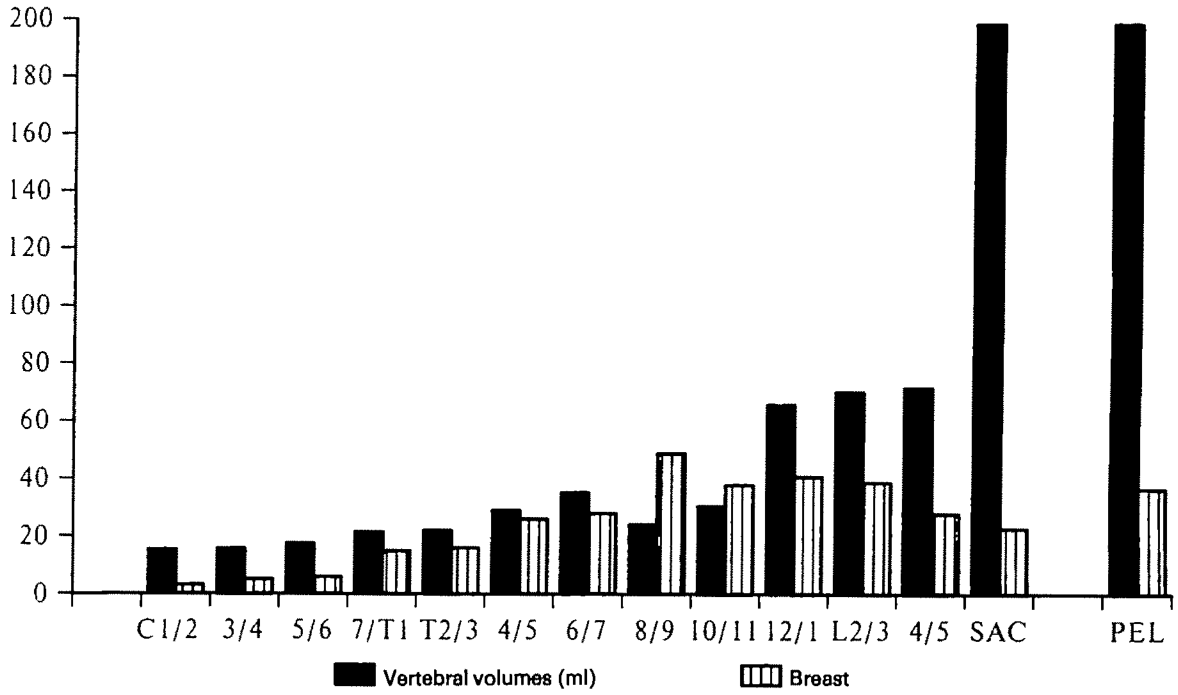

Fig. 4 The number of metastases from carcinoma of the breast in the vertebrae has been compared with the volume of the vertebrae This shows that the number of metastases is not related primarily to the amount of bone present.

veins, dural venous plexus, diploic veins, extracranial venous plexus, longitudinal vertebral veins and bones of the spine, the intercostal veins and azygos vein, lumbosacral vein and prostatic plexus, to name the more important components relevant to this study. Blood ebbs and flows with changes in intrathoracic pressure and straining forces blood out of the caval venous system and into the vertebral venous system.

We have shown that the site of metastases both in prostate and breast is not primarily related to the amount of bone and that there are differences in the distribution of these metastases. Our present knowledge of the existing circulatory systems and the vertebral venous system in particular makes it reasonable to conclude that the vertebral venous system is instrumental in the conduction of malignant cells to their bony site of metastasis not only for the prostate but also for the breast.

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The Authors

J. Cumming, ChM, FRCSE, Senior Registrar in Urology.
N. Hacking, BSc, MRCP, FRCR, Senior Registrar in Radiology.
J. Fairhurst, MRCP, FRCR, Senior Registrar in Radiology
D. M Ackery, MA, MB, DSc, FRCR, Professor of Nuclear Medicine.
J D. Jenkins, MChir, FRCS, Consultant in Urology

Requests for reprints to J. Cumming, Department of Urology, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.

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Increased Survival of Patients with Massive Lymphadenopathy and Prostate Cancer: Evidence of Heterogeneous Tumour Behaviour

D. P. S. SANDHU, P. E. MAYOR, P. SAMBROOK and N. J. R. GEORGE

Departments of Urology and Radiology, University Hospital of South Manchester, Manchester

Summary—The survival of patients with prostate cancer and radiologically detectable lymph node enlargement has been studied prospectively over an 8-year period. Computed tomography in 108 patients presenting with symptoms, signs or biochemical results suggesting lymphatic spread revealed pelvic or abdominal node masses in 60 patients; in 29 (48%), the masses measured more than 4 cm and the maximum node diameter was 15 cm. Two-thirds of patients had advanced (T3/T4) tumour stage.

Following treatment, actuarial survival in all 60 patients with nodal enlargement was 40% at 5 years. Within this group, survival in 22 patients with lymphadenopathy but negative bone scans at diagnosis was significantly better than that of 38 patients with both node and bone disease (70% vs 20% at 5 years). This improvement was related both to an apparent inability of certain tumours initially to progress and seed within bone and to a marked sensitivity of the node masses to subsequent hormonal manipulation. Primary tumour grade was proportionally similar in both groups. Unexpectedly, 6 of the 38 patients with combined disease obtained a complete remission after treatment.

The reason for this heterogeneous biological behaviour remains unclear; but these observations underscore the importance of vigorous treatment in all patients with advanced lymph node disease.

The behavioural pattern of prostatic cancer is poorly defined, as is the reaction of the individual to the disease process (Whitmore, 1973). Whilst many authorities concur with this assessment, emphasising phenotypic diversity (Fidler and Hart, 1982) and heterogeneity of metastatic potential (Kerbel, 1979), more recent studies have emphasised the highly predictable nature of the disease in which the patient's prognosis can be related to primary tumour volume and capsular invasion (McNeal *et al.*, 1986). Other specialists, however, emphasise that neither tumour volume nor grade predict progression (Epstein *et al.*, 1986), whilst occasional objective reports of atypical modes of spread (McCullough *et al.*, 1974), the finding of bony metastases in 14% of patients with palpably benign (TO) glands (Beynon *et al.*, 1983) and the selective predilection of cell lines expressing p21 ras oncogene product to metastasise to bone (Fan, 1988) suggest that not all prostate cancers will exhibit uniformity of cellular behaviour.

During prospective studies into the natural history of the disease (George, 1988), it was observed that some patients with massive nodal enlargement had no scintigraphic evidence of bone metastases and obtained a remarkable response to hormone manipulation; to investigate further this paradoxical pattern of tumour behaviour a prospective study was undertaken into the results of treatment of patients with prostate cancer associated with clinically or radiologically detectable lymph node disease.

Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Patients and Methods

Within South Manchester, all patients with histologically confirmed prostate cancer undergo assessment by full physical examination, tests of haematological, liver and renal function, estimation of tartrate lable acid phosphatase and (since 1985) prostate specific antigen (PSA), as well as urography and bone scintigraphy with complementary plain films as indicated. Patients with symptoms or signs suggestive of lymphadenopathy—palpable nodal disease, lower limb oedema, obstructive uropathy, abnormal renal function tests, rising tumour markers (in the presence of negative bone scans) or any other unexplained finding (weight loss, malaise, anaemia, *etc*)—underwent pelvic and abdominal scanning (with full bowel preparation) on a Siemens Somatom DR 2 CT scanner. All patients with nodal or bony metastatic disease were treated by hormonal manipulation (subcapsular orchiectomy or LHRH agonist) and were followed up in the prostate cancer clinic at 6-monthly or lesser intervals until death. Patients were examined and assessed by one urologist and biochemical indices, tumour markers, urography, bone and CT scans were repeated as dictated by the progress of the disease process.

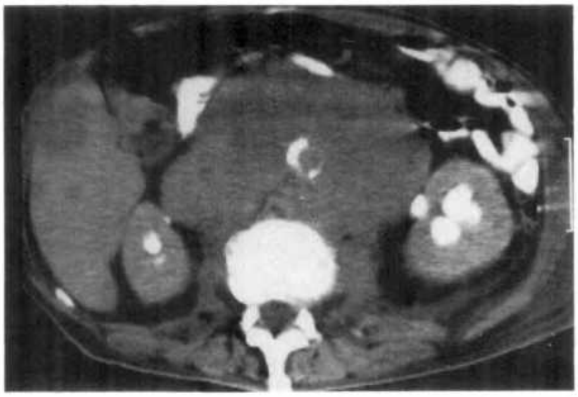

Fig. 1 CT scan showing aorta surrounded by massively enlarged nodes. Following manipulation the retroperitoneum became normal on tomography and obstructive uropathy resolved.

Results

A total of 108 patients fulfilled the criteria for CT scanning. Confident recognition of lymphadenopathy was possible when dimension exceeded 1.5 cm. Sixty patients (56%, mean age 72 years) had identifiable nodes, the diameter of which was more than 4 cm in 29 (48%) and 7 cm in 15 (25%) (Figs 1, 2A); the maximal node size was 15 cm. Primary tumour stage was advanced (T3/T4) in 41 cases (68%). Twenty-six patients had a negative CT but positive bone scans at diagnosis and in these the tumour stage was proportionally similar (T3/T4, 73%) to that of the node positive group; 22 patients with locally enlarging disease (scanned because of rising levels of PSA) were not further analysed.

Actuarial survival of all 60 node positive patients showed substantial improvement at both 2 and 5 years when compared to survival of 26 CT negative patients with bony metastatic disease or other patients with metastatic prostate cancer presenting within South Manchester (Fig. 3A). Twenty-two patients with lymphadenopathy had a negative bone scan at diagnosis. Survival in this sub-group was significantly ($P < 0.001$) better than that in the remaining 38 patients with both node and bone metastases at diagnosis (Fig. 3B), the improvement

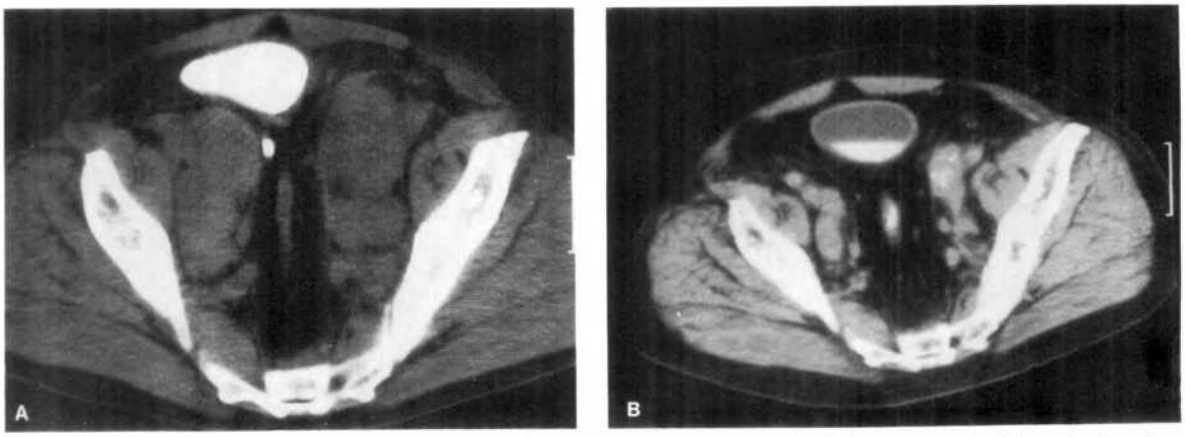

Fig. 2 (A) CT scan demonstrating enlarged pelvic nodes compressing bladder; obstructive hydroureter on the right and no function on the left. (B) Identical cut on CT scan 1 year later showing resolution of nodal disease.

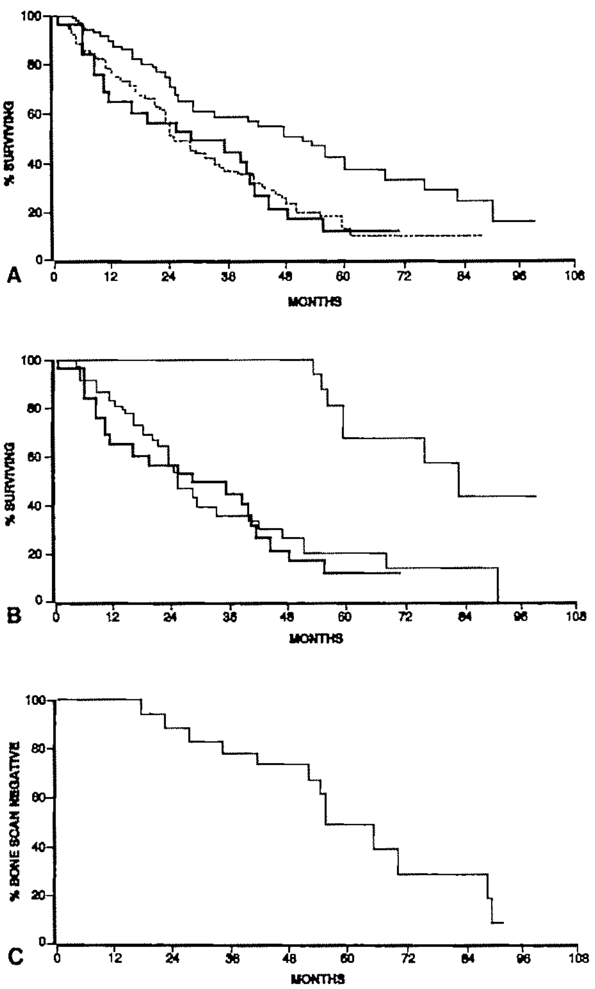

Fig. 3 Survival and progression in patients with prostate cancer and marked lymphadenopathy. (A) Actuarial survival of 60 patients with enlarged nodes (solid line) compared to 26 patients without detectable nodes but with positive bone scans (bold line) and 154 other patients from South Manchester with positive bone scans at the time of diagnosis (dotted line; data from George 1988). (B) Actuarial survival of 22 patients with lymph node enlargement alone (upper solid line) compared to 38 patients with disease in both node and bone (lower solid line) and 26 patients described above (bold line). (C) Time to progression (bone scan becomes positive) in 22 node-only patients treated by hormonal manipulation at the time of diagnosis

being related to an extraordinary response to hormonal manipulation (Fig. 2B) and subsequent prolonged progression time to bony metastatic disease (50% at 5 years) (Fig. 3C). Histological analysis of primary tumour could not distinguish between the 22 node only patients (36% high, 56% medium grade) and the 38 node/bone patients (34%, 44%).

Despite the generally poor prognosis of the 38 patients with combined disease, 6 obtained remarkable long-term regression of bony metastases (Fig. 4) which, taking radiological appearances, serum markers and other data into account, amounted to a complete remission of the disease process.

Discussion

During the 8-year study period, 406 cases of histologically proven prostate cancer were diagnosed in South Manchester and thus these results make no comment as to the absolute incidence of "major node disease" within this cancer population. However, whilst it is possible that some patients within the unscanned group had large nodes, the typical signs (Fig. 1), urographic features—known to be associated with enlarged nodes (Michigan and Catalona, 1977) (Fig. 2)—and other unexplained findings are likely to have led to a CT request and subsequent discovery of lymphadenopathy.

The absence of identifiable nodal tissue on CT scan does not, of course, imply disease-free node status or an altered immunological response to tumour. Micrometastases are known to occur early in locally active prostate cancer (Zincke *et al.*, 1982; Smith *et al.*, 1983; Wilson *et al.*, 1983; Gibbons *et al.*, 1989) and CT is recognised as being unable to detect such disease in a high proportion of cases (Flanigan *et al.*, 1985; Mukamel *et al.*, 1986). It seems likely that in this study—bearing in mind the patients' relatively advanced T stage—most, if not all, of the 26 cases with "negative" CT scans but bony metastases will have had metastatic lymph node disease. Hence it is likely that the presence or absence of detectable nodal pathology in patients with skeletal disease merely represents developing tumour burden identified by chance at the time the patient presents for treatment. Support for this view is provided by the equally poor prognosis (approximately 50% 2-year survival) observed in all groups with disease in bone at the time of diagnosis.

By contrast, evidence for heterogeneous tumour behaviour amongst those patients with "major node disease" was more convincing. Whilst, as stated, 38 patients with positive node and bone scans generally (see below) fared no better than the majority with bony metastases, the node positive/bone scan negative group of 22 patients enjoyed a highly significant survival advantage. Although the prolonged time to progression (Fig. 3C) of treated

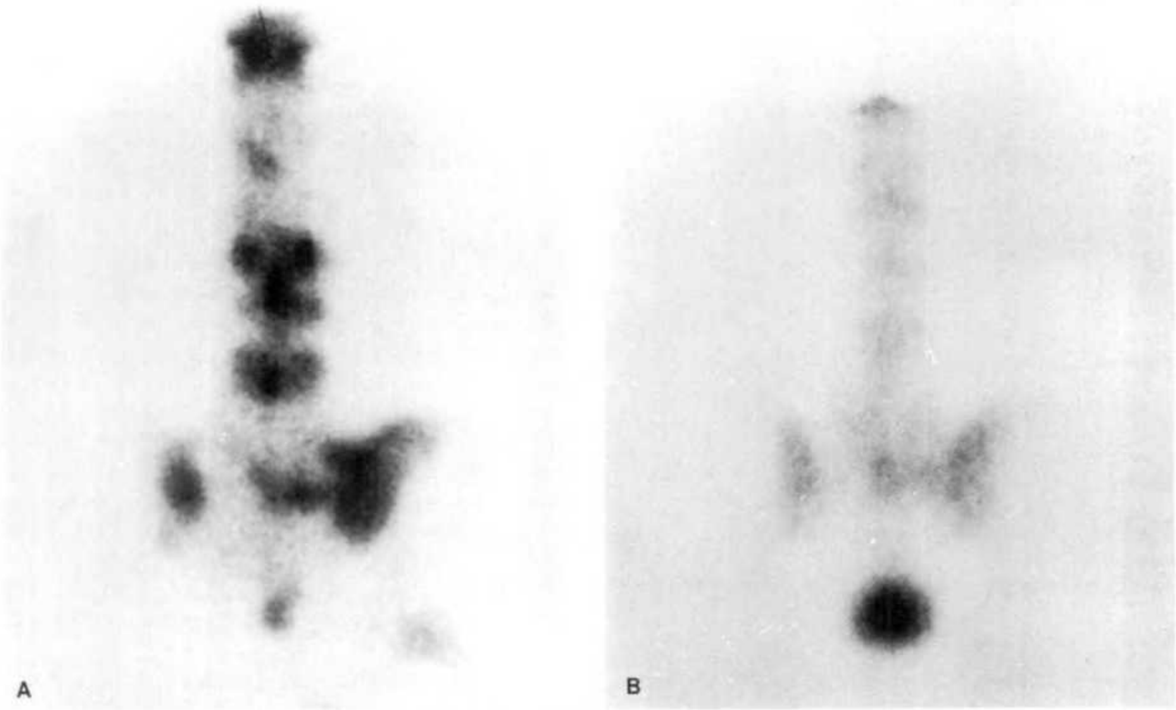

Fig. 4 (A) Patient aged 80 with both node and bone scan positive disease. (B) Forty months after hormonal manipulation this patient remains very well and in complete remission.

patients with this form of disease might in part be explained by a tumour clone with exceptional hormonal sensitivity, the critical factor conferring survival advantage to the 22 patients related to the apparent inability of their tumour cells to progress and seed within the osseous skeleton. A number had noted abdominal swelling (Fig. 1) for extensive periods prior to diagnosis, reinforcing the concept of skeletal resistance. Prostate cancer cells may produce specific growth factors (Simpson *et al.*, 1985; Fowler *et al.*, 1988; Sitaras *et al.*, 1988); whether variable expression of these or other cytokines enables or regulates spread to bone remains to be determined. Alternatively, host defence mechanisms might be aided by an inhospitable skeletal microenvironment (Manishen *et al.*, 1986) or diminished chemotaxis by tumour promoting agents (Mundy *et al.*, 1981) known to be present at the resorbing bone interface.

Remarkably, 6 of 38 patients with both node and bone infiltration responded dramatically to treatment (Fig. 4), attaining complete remission of disease. Such a favourable outcome is extremely unusual in the Manchester experience and it might be surmised that these patients were those whose cell type retained characteristics more typical of the "pure node" group and for this reason obtained a surprisingly good response to therapy. Histological review of the primary tumour, however, failed to identify any specific features which could be attributable to a particular pattern of metastasis. Only 3 abdominal node masses were biopsied at laparotomy, each showing complete replacement by prostate tumour cells; no additional comment regarding cellular response within the lymph node was possible from the available material.

This study confirms that, whilst the majority of patients with prostate cancer do progress in a predictable manner, a minority exhibit a form of heterogeneous or unexpected tumour behaviour. Detectable nodal enlargement is usually a consequence of a generalised metastatic disease process but may represent an altered host—tumour response exemplified by cellular containment within the lymphoreticular system. In clinical terms, these observations justify a policy of aggressive therapy in patients with apparently hopelessly advanced lymph node disease.

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The Authors

D P S Sandhu, FRCS, formerly Urology Registrar, University Hospital, South Manchester. Now Senior Urological Registrar, Derbyshire Royal Infirmary.

P. E Mayor, FRCR, Senior Registrar in Radiology.

P. Sambrook, FRCR, Consultant Radiologist

N J R. George, MD, FRCS, Senior Lecturer/Honorary Consultant Urologist.

Requests for reprints to. D. P. S Sandhu, Department of Urology, Derbyshire Royal Infirmary, London Road, Derby DE1 2QY.

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Persistent Carcinoma *in situ* of the Testis after Chemotherapy for Advanced Testicular Germ Cell Tumours

D. BOTTOMLEY, C. FISHER, W. F. HENDRY and A. HORWICH

Department of Histopathology and Testicular Tumour Unit, Royal Marsden Hospital, Sutton

Summary—The chemosensitivity of testicular carcinoma *in situ* (CIS) was analysed in 25 testes excised 10 weeks to 4.5 years following platinum-based chemotherapy. CIS was present in 8 of the 23 evaluable cases (35%), in 5 of which the lesion coexisted with invasive germ cell tumour. It is concluded that CIS may persist or recur after chemotherapy. This has implications for occult presentation of metastatic germ cell tumours and also for the management of the contralateral testis in patients with testicular germ cell tumours.

In the last 15 years, carcinoma *in situ* of the testis has been increasingly recognised (Skakkebaek, 1975) and its coexistence with invasive germ cell tumours of the testis documented (Jacobsen *et al.*, 1981; Coffin *et al.*, 1985). This lesion has also been documented in 5% of contralateral testes in patients with testicular germ cell tumours (Berthelsen *et al.*, 1982). The risk of a testis with CIS developing invasive tumour has been demonstrated, (Schulze and Holstein, 1977; Skakkebaek, 1978; Pryor *et al.*, 1983; Müller *et al.*, 1984) and estimated to be 40% within 3 years and 50% within 5 years (Von der Maase *et al.*, 1986b). Following chemotherapy, both persistence (Dieckmann, 1988; Von der Maase *et al.*, 1988) and eradication of CIS (Von der Maase *et al.*, 1985, 1986b) have been described in case reports and we have sought to quantify the risk. This information is germane to the management of patients with advanced germ cell tumours who have not undergone orchiectomy prior to chemotherapy. It is also relevant to patients with an invasive germ cell tumour of the testis requiring chemotherapy, who have coexistent CIS in the contralateral testis.

This study reviews the histological findings in 25 testis specimens obtained from patients presenting to the Royal Marsden Hospital between 1980 and 1988, each of whom received platinum-based chemotherapy prior to orchiectomy. The frequency of CIS in the testis and the clinical characteristics and outcome of these patients have been analysed.

Patients and Methods

Of a total of 510 men referred to the Royal Marsden Hospital between 1980 and 1988 with germ cell tumours (GCT), 25 patients were identified who had testicular surgery (24 orchiectomies and 1 testicular biopsy) more than 10 weeks after initiation of platinum-based chemotherapy. All had had clinically and/or radiologically confirmed metastatic GCT. At presentation there were 12 patients with stage IV disease, 3 with stage III, 9 with stage IIC and 1 with stage IIA disease according to the Royal Marsden Hospital staging system (Hendry *et al.*, 1980). These patients were aged between 15 and 56 years (median 30, mean 30.5).

Three of the 25 patients had had a previous GCT of the contralateral testis. One had shown clinical and ultrasonic evidence of an abnormality in the remaining testis 5 years after initial orchiectomy and treatment with BEP chemotherapy (bleomycin, etoposide, cisplatin) (Peckham *et al*, 1983) for stage IV malignant teratoma undifferentiated (MTU). Another patient presented with stage IIA MTU after an orchiectomy 1 year previously for stage I seminoma. After the diagnosis was made from lymph node biopsy the patient received CEB

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chemotherapy (carboplatin, etoposide, bleomycin) (Horwich *et al.*, 1989b) followed 5 months later by biopsy of the remaining testis. The other patient presented with stage III seminoma 2 years after an orchiectomy for stage I seminoma. Six months after receiving BEP chemotherapy he elected to have the remaining clinically normal testis removed because of the risk of residual tumour remaining.

Of the remaining patients, in 16 a histological diagnosis had been obtained from an extragonadal site prior to chemotherapy; 9 had a non-seminomatous GCT and 7 had a seminoma. A diagnosis was made in the other 6 on the basis of raised serum alphafetoprotein and/or beta human chorionic gonadotrophin in association with a tumour distribution consistent with germ cell malignancy.

At the time of testicular surgery 24 patients had a residual abnormality on ultrasonic or clinical examination of the testis. The other patient requested orchiectomy as outlined previously. Sixteen right and 9 left testis were examined histologically by one of us (C.F.).

All patients received 1 or more chemotherapy regimens which contained cisplatin or carboplatin, including PVB (cisplatin, vinblastine, bleomycin) (Einhorn and Williams, 1980), BEP, CEB and BOP (bleomycin, vincristine and cisplatin) (Horwich *et al.*, 1989a). The interval from the beginning of chemotherapy to orchiectomy ranged from 11 to 238 weeks (mean 42.5, median 22). The follow-up period from orchiectomy to either the death of the patient or to the time of analysis ranged from 2 to 87 months (mean 29.5, median 18).

Results

Histology

Of 25 testes, 23 were assessable for the presence or absence of CIS using the criteria of Skakkebaek (1975). The 2 other testes contained malignant teratoma trophoblastic (MTT) and malignant teratoma intermediate (MTI) respectively and no seminiferous tubules could be identified.

Table 1 Testis Histology Related to Metastasis and Outcome

Testis histology	*No. of patients*	*No with metastasis at time of orchiectomy*	*No. of deaths*
CIS only	3	1	1
CIS + invasive tumour	5	1	1
Invasive tumour (CIS not assessable)	2	2	2
No tumour	15	3 (1*)	4

*Probable but unproven metastasis.

The numerical breakdown into histological categories is shown in Table 1. Of the 23 testes which could be assessed, CIS was present in 8 (35%); 5 of these contained invasive tumour (4 seminomas, 1 MTU) in addition to CIS, while the remaining 3 contained CIS alone. Overall, 7 of 25 testes (28%) contained invasive tumour with or without CIS.

All but 1 of the testes containing CIS and/or invasive tumour were the original primary sites of tumour prior to chemotherapy. The 1 other testis which contained CIS plus seminoma was the contralateral testis of a man treated with 4 courses of BEP chemotherapy for stage IV MTU 5 years previously.

In Table 2 some of the characteristics of those patients with residual CIS testis after chemotherapy are shown. There was no obvious distinguishing feature of this group compared to the group of 25 as a whole. They presented with a variety of stages of disease, differing original histology and were exposed to a variety of chemotherapy regimens prior to histological examination of testes.

Spermatogenesis was seen in 3 of the 23 assessable testes. All 3 contained CIS plus invasive tumour as well.

Relationship of testicular histology to interval between chemotherapy and orchiectomy

An analysis was performed to determine whether there was any relationship between the chemotherapy to orchiectomy interval and presence of CIS. The 2 testes which were not assessable for CIS were excluded. In addition, the 2 testes that had been the "normal contralateral testis" at the time of chemotherapy were excluded since it was not known whether CIS was present at that time. On the other hand, the abnormal testes which contained primary tumour were very likely to have had CIS at the time of chemotherapy (Jacobsen *et al.*, 1981). This large series of testicular tumours showed that the incidence of CIS was 88.6% in association with seminoma and 99.2% in association with non-seminomatous GCTs.

The mean interval between the initiation of chemotherapy to orchiectomy for testes with CIS ± invasive tumour was 46.8 weeks (SD = 44.0) (n = 7, range 12–141) and the interval for testes without CIS was 31.4 weeks (SD = 22.7) (n = 14, range 11–86). This difference was not statistically significant at the 5% level using Student's *t* test analysis.

Table 2 Characteristics of Patients with CIS Testis after Chemotherapy

Patient	*Age (years)*	*Testis histology*	*Chemotherapy (courses)**	*Previous histology*	*Stage at presentation†*
1	22	CIS+seminoma	BEP (4)	MTU (other testis)	IV (MTU) I (seminoma)
2	22	CIS+seminoma	PVB/BEP (6) VAC (2)	MTU	IV
3	30	CIS	CEB (4)	Serum markers elevated	IV
4	25	CIS+seminoma	BEP (4)	Seminoma	IIC
5	28	CIS	CEB (4)	MTU	IV
6	33	CIS+seminoma	Carboplatin (6)	Seminoma	III
7	18	CIS	CEB (4)	MTU (contralateral seminoma)	IIA I (seminoma)
8	34	CIS+MTU	CEB (4) PVB (2) VAC (2)	MTU	IIC

*For chemotherapy regimes, see text.
In addition VAC = vincristine, actinomycin D, cyclophosphamide
†Royal Marsden Hospital Staging System.

Relationship of testicular histology to metastatic disease and eventual outcome

Table 1 shows the relationship of testis histology to metastatic tumour and outcome at the time of orchiectomy. Evidence of viable metastatic disease was based on obtaining positive tumour histology on biopsy from an extragonadal site and/or demonstrating rising serum tumour markers after orchiectomy. Seven patients (28%) had metastatic disease at the time of orchiectomy, 3 based on histological confirmation and 4 on persistently raised tumour markers with or without a persistent radiological abnormality. All 7 patients later died from disseminated malignancy. There was 1 further death after tumour relapse of a patient with no tumour in the testis and an apparently resolving abdominal mass which was shown to contain viable tumour after a subsequent biopsy.

Three (all non-seminomatous GCT) of 7 patients with residual invasive tumour in the testis after chemotherapy had good evidence of persisting disease at other sites also. One patient who had CIS without invasive tumour in the testis had coexisting metastatic tumour at the time of orchiectomy.

Three of 15 patients (20%) with apparent eradication of tumour within the testis had metastatic tumour at the time of orchiectomy and 1 patient (seminoma) with no tumour in the testis was shown, 7 months later, to have viable tumour within an abdominal mass which had been slowly resolving up to this point.

There were 4 patients with no extragonadal tumour after chemotherapy despite the presence of invasive tumour (all seminoma) within the testis.

Discussion

In the majority of patients presenting with a GCT of the testis, the testicular tumour is palpable and can be judged both clinically and by ultrasonography to be malignant. A definite diagnosis (and often cure in the case of a stage 1 tumour) can be obtained by orchiectomy.

There are situations where a patient may present with metastatic disease from which histological confirmation of germ cell malignancy is made. Retrospectively, an abnormality in the testis may be discovered after chemotherapy has begun. Furthermore, occasionally, in a life-threatening situation, chemotherapy is started before histological confirmation is obtained, and again if there is complete response of extragonadal tumour, there is a dilemma regarding the requirement for a post-chemotherapy orchiectomy (Greist *et al.*, 1984).

It has been argued that an orchiectomy should be performed because of the risk of a differential response of tumour to chemotherapy between testis and extragonadal sites (Fowler and Whitmore, 1981; Greist *et al.*, 1984; Chong *et al.*, 1986). Our results add supportive evidence to this claim. A total of 7 patients had good evidence of persistent metastatic disease after chemotherapy while 10 (3 with CIS alone, 7 with invasive tumour ± CIS) had confirmed malignancy within the testis. There were also 3 patients with eradication of tumour from the testis but with persisting metastatic disease. This disparity of testis and extratesticular tumour response to chemotherapy has been documented previously (Chong *et al.*, 1986). The major hypotheses for this variable response are the presence of a blood-testis barrier, and tumour heterogeneity as a result of spontaneous mutation as discussed by Chong *et al.* (1986). In addition to these factors, CIS of the testis may independently possess resistance to chemotherapy, possibly because of its site within seminoferous tubules or an inherent characteristic of the cells themselves.

CIS may be temporarily suppressed, but not eradicated, by chemotherapy in an analogous way to spermatogenesis after chemotherapy (Rudy, 1989). It is interesting to note that only 3 testes showed spermatogenesis in our series and all were associated with the presence of CIS and invasive seminoma. As reactivation of spermatogenic cells occurs, one may speculate that the same conditions are present for the recovery of CIS. Although CIS and spermatogenesis coexisted in 3 specimens, 5 testes with CIS had no evidence of spermatogenesis, which may suggest that CIS is more resistant to chemotherapy than normal testis germ cells. However, normal germ cells may already be absent in association with CIS or invasive tumour before chemotherapy is administered (Schulze and Holstein, 1977; Krabbe *et al.*, 1979).

The conclusion from this study is that CIS has a substantial resistance to standard chemotherapy regimens. The implications for clinical management are that orchiectomy is necessary, despite apparent complete extragonadal response to chemotherapy, if an abnormality is present in one of the testis. Where a testicular tumour is not detectable, especially if there are retroperitoneal metastases, the management should include frequent follow-up with testicular palpation, ultrasound and probably biopsy also (Berthelsen *et al.*, 1982; Daugaard *et al.*, 1987; Dieckmann and Bauer, 1987).

The frequency of residual CIS after chemotherapy in our series plus previous reports of sequential bilateral GCTs despite interval chemotherapy (Fowler *et al.*, 1979; Dieckmann, 1988) make it advisable to recognise the risk of a future contralateral testicular tumour. It may be wise to look for CIS in the contralateral testis when a patient first presents with a testicular tumour, especially if there is a history of maldescent (Von der Maase *et al.*, 1986b). If CIS is present, chemotherapy cannot be relied upon to eradicate it. However, the possible eradication of CIS by radiotherapy (Von der Maase *et al.*, 1986a) may provide an alternative approach to radical surgery for this condition.

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The Authors

D. Bottomley, MB, MRCP, Senior House Officer
C Fisher, MA, MD, FRCPath, Consultant Histopathologist.
W F. Hendry, ChM, FRCS, Consultant Urological Surgeon.
A. Horwich, PhD, MRCP, FRCR, Professor of Radiotherapy.

Requests for reprints to: A. Horwich, Testicular Tumour Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT

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The Importance of Prognostic Factors in the Individual Treatment of Patients with Disseminated Germ Cell Tumours

P. F. A. MULDERS, G. O. N. OOSTERHOF, C. BOETES, P. H. M. DE MULDER,
A. G. M. THEEUWES and F. M. J. DEBRUYNE

Department of Urology, St Radboud University Hospital, Nijmegen, The Netherlands

Summary—Following chemotherapy for disseminated testicular cancer, 55 patients underwent surgery because of residual tumour. The histological findings were viable tumour in 12 patients, mature teratoma in 12 and fibrosis and/or necrosis in 31. Retroperitoneal abdominal masses were evaluated radiographically before and after chemotherapy. The reduction in size of these masses after chemotherapy appeared to have prognostic significance. A decrease of more than 70% was always associated with fibrosis. A residual mass over 50 mm indicated viable tumour or mature teratoma. Seminoma or embryonal carcinoma was more likely to result in fibrosis/necrosis in the resected tissue. Both the Indiana and the EORTC classification models can be used for prognosis.

Radiographic measurements before and after chemotherapy are of considerable prognostic significance. These objective indicators help in planning treatment and so diminish the side effects of therapy and maintain or even increase the high cure rate in disseminated testicular cancer.

Testicular cancer should now be curable even in an advanced stage. Cure rates of 70 to 80% have been reported for disseminated germ cell tumours of the testis. The introduction of cisplatin-based combination chemotherapy has increased cure rates dramatically (Einhorn and Donohue, 1977; Stoter *et al.*, 1984). Improvements in staging methods and surgical techniques are also relevant to cure rates (Javadpour *et al.*, 1982; Loehrer *et al.*, 1986). Despite the encouraging results, we need a better insight into the timing and extent of the different phases of treatment.

The European Organization for Research and Treatment of Cancer (EORTC) classification of prognostic factors, together with Indiana classification of extent of disease, defined risk factors for individual patients at the start of treatment (Birch *et al.*, 1986; Stoter *et al.*, 1987). The number of cycles of chemotherapy is, however, usually prearranged and subsequent surgery is standard when residual tumour is present.

The purpose of this study was to look for other prognostic factors that might help to define a more individual treatment schedule and thus diminish the side effects of therapy and increase cure rates.

Patients and Methods

Between January 1979 and January 1988, primary chemotherapy was given to 61 patients with disseminated germ cell tumours. The histology of the primary tumour was non-seminoma in 46 cases and seminoma in 15; 3 of these were extragonadal tumours. The extent of disease was established according to the Royal Marsden classification (Peckham *et al.*, 1979). Included were stages IIc, III and IV. Chemotherapy before surgery consisted of 4 or more cycles of cisplatin-based combination therapy (cisplatin, vinblastine, bleomycin (PVB), bleomycin, etoposide, cisplatin (BEP) or PVB and BEP alternating); 51 patients received 4 cycles of chemotherapy and 10 patients received up to 8 cycles before surgery because tumour markers remained high. The patients were staged retrospec-

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tively according to the Indiana classification of extent of disease and the EORTC classification of prognostic factors (Birch *et al.*, 1986; Stoter *et al.*, 1987).

After chemotherapy, all patients were evaluated by clinical, biochemical and radiological examination. Biochemical assessment included serum α-fetoprotein (α-FP, normal <20 ng/ml) and human chorionic gonadotrophin (β-HCG, normal <3.0 ng/ml).

Radiological examination consisted of abdominal computed tomography (Siemens Samatron DR3), chest X-ray and lung tomography. Radiological re-evaluation was done by one radiologist (C.B.). The cure rate, 3-year survival rate and histopathological outcome of surgery were established in relation to the 2 classifications. Following chemotherapy, surgery was performed in the 55 patients with residual tumour. Residual mass was defined as nodes >10 mm and/or residual strands on computed tomography. Five patients had no residual mass after chemotherapy and normal tumour markers; they were followed up closely. One patient died soon after establishment of the diagnosis. The operation in patients with residual mass after chemotherapy consisted of retroperitoneal lymph node dissection (RPLD) in 44 patients, thoracotomy in 6 and both in 5 patients. Resected residual tumours were examined histologically. Patients with fibrosis or mature teratoma were followed up closely at lengthening intervals. Patients with viable tumour in the resected tissue were given additional chemotherapy.

The size of metastatic tumour before and after chemotherapy was measured radiologically (largest transverse diameter) and compared with the histopathological assessment.

Cure was defined as absence of biochemical or radiological evidence of disease after chemotherapy or as a surgical finding of fibrosis or mature teratoma (the latter only if all residual tumour mass had been removed). Follow-up ranged from 5 months to 8 years (mean 3 years). The accuracy of the classifications was analysed statistically by the Kaplan-Meier method for survival and cure rates, and significance was estimated with trend tests. Differences in histological outcome were analysed by the χ^2 test; in the case of continuous variables, the Kruskal-Wallis test was used.

Results

The overall 3-year survival rate of 61 patients with disseminated germ-cell cancer was 78% and the cure rate was 72%. Patients were placed in the subgroups of the EORTC classification (good, moderate or bad prognosis) and the Indiana model (minimal, moderate, advanced disease). Survival and cure rates were calculated for the patients in the subgroups of the 2 classifications (Tables 1 and 2). Both methods of classification correlated well with cure and survival rates.

The histological assessment of specimens was of great importance for 3-year survival: 31 patients had fibrosis or necrosis or both, 12 had mature teratoma and 12 had viable tumour. The 3-year survival rates for these groups are shown in Table 3. The histology of the primary tumour was important for the results of surgery; seminoma or embryonal cell carcinoma was more likely to produce fibrosis or necrosis (Table 4). Two patients

Table 1 Prognostic Classification and Cure Rate

		No.	*Cure rate (%)*	
EORTC	good	18	94	
	moderate	30	77	$P=0.029$
	poor	13	62	
Indiana	minimal	17	88	
	moderate	28	79	$P=0.017$
	advanced	16	69	

Table 2 Prognostic Classification and Survival

		No.	*3-year survival (%)*	
EORTC	good	18	100	
	moderate	30	78	$P=0.006$
	poor	13	51	
Indiana	minimal	17	89	
	moderate	28	76	$P=0.09$
	advanced	16	69	

Table 3 Histological Results and Survival

	No	*3-year survival rate (%)*	
Fibrosis	31	93	
Teratoma	12	92	$P<0.001$
Tumour	12	27	

Table 4 Histology of Primary Tumour in Fibrosis Group

	No.
Seminoma	9
Malignant teratoma undifferentiated	4
Malignant teratoma	1
Malignant teratoma trophoblastic	1

with fibrosis died, 1 from brain metastases and 1 from a malignant Leydig cell tumour. Only 1 patient died post-operatively after resection of a 30-cm abdominal tumour (mature teratoma). Of the 12 patients with viable tumour in the residual mass, 7 died from testicular cancer. The 5 patients with no residual tumour after chemotherapy and who were not operated on are still alive with no evidence of disease.

The relative reduction in tumour mass after chemotherapy had great significance. The median decrease was 70% in patients with a histological outcome of fibrosis and 28% in the group with mature teratoma or tumour (Table 5). The difference was statistically significant.

In 5 patients the abdominal mass increased during chemotherapy; 4 had mature teratoma and 1 had viable tumour. We found that a reduction of more than 70% was always associated with a histological report of fibrosis (Table 6).

The size of residual mass after chemotherapy and the histological assessment are shown in Table 7. Even in small residual tumours, viable tumour could be found, although rarely. Large residual tumours were more likely to contain mature teratoma or viable tumour. This was always the case for residual masses >50 mm. When Tables 5 and 6 are combined, the results shown in the Figure are obtained.

Elevated tumour markers (α-FP and/or β-HCG) following chemotherapy were also of prognostic importance. Three patients with persistently high α-FP or β-HCG after chemotherapy underwent surgery. They all had viable tumour in the resected tissue, but 9 patients with normal levels of tumour markers still had viable tumour in the resected tissue.

Table 5 Size of Tumour and Results of Operation

	Median size (mm) before		*Median difference*	
	Chemotherapy	*Surgery*	*Absolute (mm)*	*Relative (%)*
Fibrosis	75	20	40	70
Teratoma	63	53	3	10
Tumour	100	53	40	50
	P=0 08	*P*<0.001	*P*=0.003	*P*<0 001

Table 6 Relative Decrease on CT Scan and Histological Assessment

Decrease	*No*	*Fibrosis*	*Teratoma*	*Tumour*
>30%	36	28	2	6
>50%	24	19	2	3
>70%	15	15	0	0

Table 7 Size and Histological Assessment

Size (mm)	*No.*	*Fibrosis (%)*	*Teratoma (%)*	*Tumour (%)*
0–20	20	85	10	5
21–30	9	78	11	11
31–50	9	56	22	22
>50	9	0	55	45
Total	47	62	22	16

Discussion

Disseminated testicular cancer can be cured in most cases with a combination of chemotherapy and surgery. It is, however, difficult to predict the results of treatment in individual cases. The EORTC classification of prognostic factors and the Indiana classification of extent of disease attempt to categorise patients in order to predict the efficacy of treatment. Multivariate analysis leads to the formation of prognostic groups that indicate response rates and survival rates (Medical Research Council Working Party on Testicular Tumours, 1985; Birch *et al.*, 1986, Stoter *et al.*, 1987; Droz *et al.*, 1988). In the present series the EORTC classification was more appropriate. Standard therapy for disseminated testicular carcinoma is the same, whatever the risk: 4 cycles of combination chemotherapy followed by resection of residual

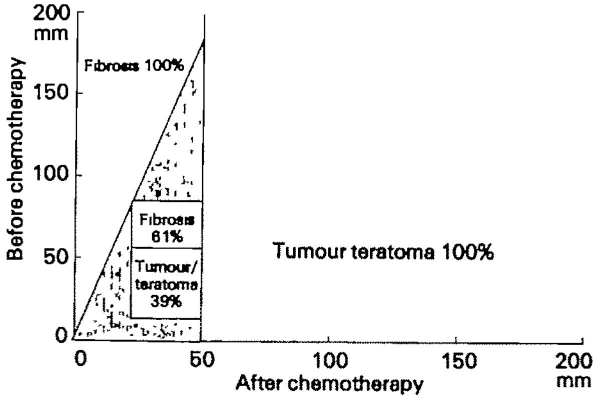

Fig. Tumour size (mm) before and after chemotherapy in relation to the histological outcome.

mass. The detection of prognostic factors should result in more individualised treatment.

Individualised chemotherapy might consist of fewer cycles for patients with good prognostic factors and more cycles (with more effective and probably more toxic chemotherapy) for those at high risk.

With regard to the best individual treatment, the role and timing of cytoreductive surgery are of special interest. Standard treatment includes surgery when a residual mass remains after chemotherapy (Donohue *et al.*, 1980, 1984), but should every patient with residual tumour, however small, undergo surgery?

Survival rates depend largely on the histology of resected specimens (Einhorn *et al.*, 1981; Donohue *et al.*, 1982). A patient with residual viable tumour or mature teratoma should undergo surgery in order to reduce the size of the tumour and make it accessible to secondary chemotherapy, since it could grow or become malignant again (Logothetis *et al.*, 1982; Suurmeijer *et al.*, 1984). Fibrosis or necrosis need not be resected.

Donohue *et al.* (1987) showed that the histology of the primary tumour was an important prognostic sign for the outcome of RPLD. Tumours without teratomatous elements were more likely to lead to fibrosis in the resected tissue. Our data also showed that the absence of teratomatous elements in the primary tumour was more likely to produce fibrosis in the residual mass, especially when combined with a marked reduction in size of the abdominal mass during chemotherapy.

Unlike other workers (Friedman *et al.*, 1985; Stanton *et al.*, 1985), we found that the residual mass after chemotherapy for disseminated pure seminoma could contain viable tumour. This was found in 4 of 15 patients with pure seminoma. Motzer *et al.* (1987) reported similar results. The reduction of retroabdominal metastatic tumour after chemotherapy appeared to be of value. A relative decrease of more than 70% was always associated with fibrosis in our patients. The reduction was significantly less in patients with residual viable tumour or mature teratoma. A residual mass >50 mm was associated with mature teratoma or viable tumour. Mature teratoma was often found after an increase in metastatic mass during chemotherapy. However, even in the smallest residual mass, viable tumour cells could be present. Other investigators did not find such a clear correlation between radiological findings and histological outcome (Husband *et al.*, 1982; Stomper *et al.*, 1985).

Although we operated on a relatively large number of patients after chemotherapy, it is unwise to generalise from a small study group. Prospective studies with large numbers of patients will give more insight into this important issue.

It was concluded that the relative reduction in size of metastases in patients on chemotherapy and the size of the residual mass after chemotherapy are significantly related to the histological outcome; the histology of the primary tumour is also of prognostic importance. Prospective trials should be undertaken to find out if chemotherapy could be reduced when there is a rapid reduction in tumour volume and no teratomatous elements in the primary tumour, and if prolonged chemotherapy might obviate the need for surgery in other cases by bringing about complete remission.

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The Authors

P F A Mulders, MD, Urological Research Fellow.
G. O N. Oosterhof, MD, Consultant in Urology.
C. Boetes, MD, Consultant in Radiology
P H. M. de Mulder, MD, PhD, Consultant in Medical Oncology.
A G. M Teeuwes, PhD, Statistician.
F. M J Debruyne, MD, PhD, Professor and Chairman, Department of Urology.

Requests for reprints to: F. M. J. Debruyne, Department of Urology, St Radboud University Hospital, P O. Box 9101, 6500 HB Nijmegen, The Netherlands.

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Case Reports

Vesicocutaneous Fistula Secondary to Bladder Instability

J. P. MacDERMOTT, J. M. PALMER and A. R. STONE,
Department of Urology, University of California, Davis,
Sacramento, *USA*

Post-operative vesicocutaneous fistulae should close without further intervention after a period of catheter drainage. We present a case of persisting fistula despite repeated attempts at long-term catheter drainage and surgical excision.

Case Report

A 50-year old white female diabetic presented with urinary incontinence in 1976. Stress incontinence was diagnosed and a Marshall-Marchetti-Krantz repair performed. Some months later she developed urinary retention, which was attributed to a diabetic neuropathy. An attempt at take-down of the MMK repair was unsuccessful because of fibrosis. YV-plasty of the bladder neck was performed and immediately after this she developed a fistula from the bladder to the abdominal wall. This fistula eventually closed following 3 weeks of catheter drainage. On removal of the catheter the fistula recurred, however, and the sequence was repeated unsuccessfully on 3 subsequent occasions. Surgical excision of the fistulous tract was performed in 1982, with closure of the bladder defect, but this also failed. Following a further period of catheter drainage which appeared to close the fistula, the patient was commenced on intermittent catheterisation. Despite this, the fistula recurred yet again (Fig. 1).

On presentation to this department the patient had an indwelling Foley catheter with no leakage from the fistula. She complained of bladder spasms with the catheter *in situ* and admitted to frequency, nocturia, urgency and urge incontinence each time it had been removed. A cystometrogram showed a grossly unstable bladder. She was unable to initiate a detrusor contraction voluntarily and voided inefficiently by abdominal strain. Cystography demonstrated Grade III vesicoureteric reflux on the right.

Treatment with Ditropan was initiated but she developed severe side effects and this was discontinued. In view of her high detrusor pressures, it was felt that she would probably not respond to other anticholinergics and it was decided to modify her bladder behaviour surgically. The procedure included excision of the fistulous tract, clam ileocystoplasty, split-cuff right ureteric reimplantation and omental wrap. The previous Marshall-Marchetti repair was taken down and the bladder neck resuspended by the obdurator shelf suspension method. Recovery was uneventful and cystography prior to removal of the suprapubic tube showed an adequate cystoplasty volume with no reflux (Fig. 2). The patient is now fully continent without urge symptoms; she carries out intermittent catheterisation and has had no recurrence of her fistula.

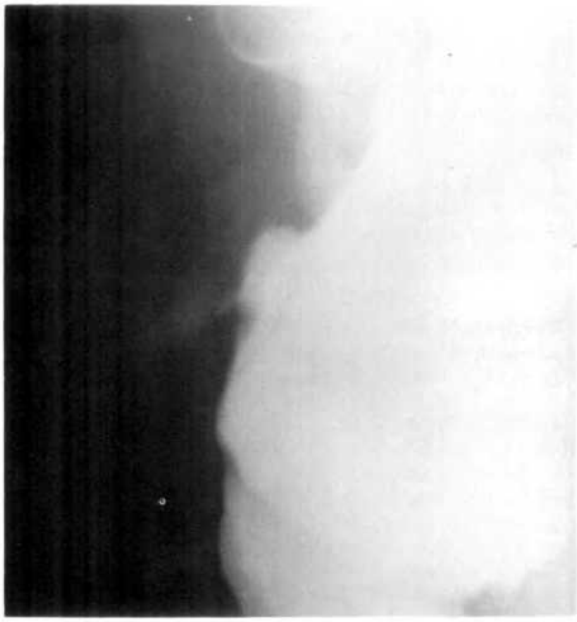

Fig. 1 Cystogram showing origin of fistulous tract on left.

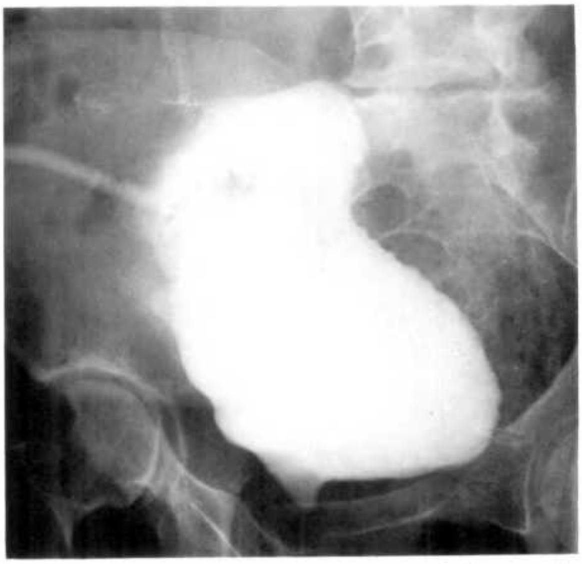

Fig. 2 Post-operative cystogram prior to removal of suprapubic catheter.

Comment

The combination of high pressure detrusor instability, ureteric reflux and inability to initiate a voluntary detrusor contraction suggest a neuropathic aetiology. This was probably the major cause of the patient's initial incontinence rather than any stress element. This instability would certainly have been exacerbated by the relatively obstructive Marshall-Marchetti repair, with high pressure plus relative outflow obstruction causing persistence of the fistula.

This case illustrates the importance of fully establishing the cause of incontinence prior to surgery (Byrne *et al.*, 1987). Any suspicion of an urge component calls for urodynamic assessment. It also emphasises the importance of complete excision of the fistulous tract and the provision of low bladder pressure to facilitate healing.

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Requests for reprints to. J. P MacDermott, Department of Urology, 4301 X Street, Sacramento, California 95817, USA

Gastric Carcinoma Presenting as Urinary Retention

C. J. E. WATSON and P. T DOYLE, *Department of Urology, Addenbrooke's Hospital, Cambridge*

Case Report

A 68-year-old man presented with a 2-year history of deteriorating urinary stream and increasing frequency of micturition. At the time of admission he was passing urine 2-hourly day and night. There was no associated dysuria or haematuria.

Fourteen years previously he had undergone a partial gastrectomy for a signet ring carcinoma of the stomach with lymph node metastases. Abdominal examination at admission was unremarkable. Rectal examination revealed a hard, irregular prostate.

He underwent transurethral resection of the prostate and histological examination showed it to be a signet ring carcinoma (cytokeratin stain was positive, prostate specific antigen negative) compatible with a secondary from his original gastric primary.

Comment

Malignant neoplasms of prostate are usually primary adenocarcinomas. Secondary prostatic neoplasms are usually due to direct invasion by neighbouring tumours (*e.g.* bladder and rectum). Excluding direct invasion, secondary prostatic neoplasms are uncommon and rarely diagnosed prior to death. However, this case illustrates the significance of an alternative primary and the different treatment requirements are obvious. There are few other case reports of stomach metastasising late to the prostate. Johnson *et al.* (1974) reviewed 1474 patients with prostatic neoplasms and found 18 (1.2%) to be metastatic neoplasms, with only 1 patient having a gastric primary. Of the 18 patients only 3 presented before death, and all with obstructive symptoms. Thompson *et al.* (1953) reported another case metastasising to the prostate 4 years after a partial gastrectomy and in a review of 5000 autopsies Klinger (1951) found no case of stomach metastasising to prostate, although pancreatic, lung and lymphoreticular neoplasms were common.

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Requests for reprints to· C. J E Watson, Department of Surgery, Level 9, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

Thirteen-year Survival of Patient with Recurrent Metastatic Renal Carcinoma

M. F. VAN DRIEL and H. J. A MENSINK, *Department of Urology, University Hospital, Groningen, The Netherlands*

Case Report

In December 1976 a 59-year-old Caucasian female underwent a right radical tumour nephrectomy. Lymph nodes were negative. Microscopy showed a pleomorphic tumour and irregular nuclei with prominent nucleoli. Most cells contained clear cytoplasm. In 1983, 2 subcutaneous nodules on her back were excised. Histological examination showed metastatic renal carcinoma. By 1989, 34 such subcutaneous metastases have been removed under local anaesthesia, mainly for psychological reasons in the absence of metastatic disease elsewhere. Two very slow growing pulmonary metastases have recently become visible on chest X-ray. Bone scans are negative. The patient remains in good condition and has no complaints

Comment

Renal carcinoma is notorious for metastasising many years after the primary tumour has been removed, and these metastases occasionally grow very slowly. The prognosis improves progressively with longer intervals between nephrectomy and the subsequent appearance of metastases (O'Dea *et al.*, 1978). In an analysis of the autopsy records of 1828 patients with renal carcinoma there were 5 patients with metastases who had survived for 10 years or more after nephrectomy (Saitoh *et al.*, 1982). It is reasonable to assume that the clinical course of our patient was influenced more by the characteristics of the tumour itself and the competence of the patient's immune system than by the subsequent removal of metastases.

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Requests for reprints to: M. F. van Driel, Department of Urology, University Hospital Groningen, P.O Box 30001, 9700 RB Groningen, The Netherlands.

Granulomatous Hepatitis Following Intravesical BCG Therapy

D. THOMPSON and J. CUMMING, Gastrointestinal Unit and Department of Surgery/Urology, Western General Hospital, Edinburgh

A small number of cases of biopsy proven granulomatous hepatitis have been reported after intravesical therapy with Tice strain (Marans and Bekirov, 1987) and lyophilised Pasteur strain BCG (Steg *et al.*, 1985). We report a case of granulomatous hepatitis following intravesical Glaxo strain BCG despite prophylactic isoniazid.

Case Report

A 76-year-old man presented in 1967 at the age of 54 years with haematuria and a small papillomatous transitional cell carcinoma was excised by diathermy. There was no evidence of recurrence at review until 1987, when he was found to have a Grade III papillary transitional cell carcinoma. A cystogram showed bilateral ureteric reflux. He was treated with 60 mg intravesical Glaxo BCG once weekly for 6 weeks. He lived in a rural area 70 miles from this hospital and instillations were made by his family doctor. Treatment was badly tolerated and associated with severe dysuria and frequency. He was admitted routinely for cystoscopy in the middle of this course and was found to have severe granulomatous cystitis; his bladder capacity was only 150 ml.

Recurrent tumour was not evident histologically or cytologically until 5 months later. An anterior myocardial infarct at this time ruled out a cystectomy; 12 months after his first course of intravesical BCG a second was commenced. He had 60 mg of intravesical BCG weekly for 4 weeks, with 600 mg of isoniazid daily for 2 days after each bladder instillation. Treatment was associated with suprapubic pain, frequency, difficulty in voiding and haematuria. He was admitted again for routine mid-course cystoscopy and this showed marked inflammation and blood clot. Liver function tests, which had previously been normal, showed his alkaline phosphatase to be 1460 iu/l, gamma GT 697 iu/l, bilirubin 37 μmol/l and AST 172 iu/l. He was also hyponatraemic, uraemic and hypoalbuminaemic: 128 mmol/l, 16.1 mmol/l and 26 g/l respectively. Liver biopsy showed granulomas; no organisms were identified. He was treated with prednisolone 30 mg per day, rifampicin 300 mg daily and isoniazid 300 mg daily. One month later he was constitutionally improved, his electrolytes were normal and the alkaline phosphatase had fallen to 457 iu/l.

Comment

A toxic reaction to intravesical BCG is very common. However, reactions are mostly mild and self-limiting, responding to reduction or cessation of treatment. Cystitis is the most common adverse reaction, occurring in 90% of patients. Hepatic granulomas due to intravesical therapy alone are rare. In a review of 1278 patients, Lamm *et al.* (1986) reported no such cases, but 3 cases have been reported elsewhere, 1 following Tice strain BCG and 2 after lyophilised Pasteur strain BCG.

This patient developed granulomatous hepatitis despite prophylactic isoniazid. His BCG was administered in the community and it may be that closer monitoring would have revealed warning symptoms or signs that would have lead to earlier cessation of therapy.

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Requests for reprints to: D. Thompson, Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU.

Testicular Haematoma: A Delayed Complication of Testicular Vein Ligation

T. J. PODD, *Department of Urology, Freeman Hospital, Newcastle upon Tyne*

Case Report

A 25-year-old man was referred with hard, painless enlargement of his left testis. This enlargement had occurred in a series of stages, the first of which began shortly after high ligation of the left testicular vein via an inguinal approach 4 years previously as operative treatment for a left variococele. There was no history of trauma. Urgent ultrasound revealed an appearance compatible with testicular tumour with central haemorrhagic necrosis. Chest X-ray and ultrasound scan of retroperitoneal nodes were both negative. Left orchiectomy was performed via an inguinal approach. Histology revealed the presence of a large intra-testicular haematoma surrounded by a thin rim of normal testicular tissue, but no evidence of any underlying lesion.

Comment

The above would appear to represent both a rare complication of testicular vein ligation and differential diagnosis of testicular enlargement. Whilst testicular haematomas have been described in association with vascular malformations, there was no evidence of such in this case. One can only assume, therefore, that intra-testicular venous hypertension led to an initial haematoma which subsequently enlarged through repeated haemorrhages over the 4 years between the initial ligation of varicocele and orchiectomy.

No references were found describing this particular complication in the absence of a history of trauma or of an underlying vascular abnormality.

Requests for reprints to: T. J. Podd, Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN.

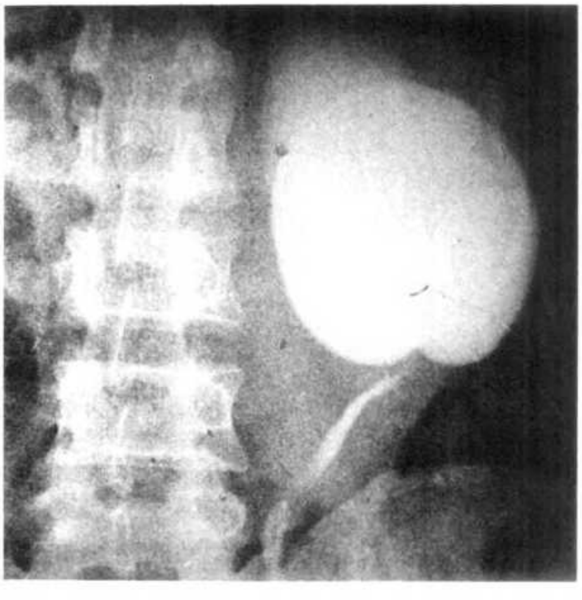
A Giant Renal Stone

F. IBRAHIM, *Department of Urology, Khartoum Teaching Hospital, Khartoum, Sudan*

Case Report

A 38-year-old man presented with left flank pain which was dull and localised. Physical examination revealed a well developed and well nourished man. No abdominal mass was palpable. A haemogram, renal function tests and metabolic studies were normal. Examination of the urine showed pyuria and microscopic haematuria. Culture grew *Escherichia coli* sensitive to trimethoprim, gentamicin and nitrofurantoin.

Intravenous urography showed a huge rounded opacity in a dilated left renal pelvis. The right kidney was normal. Ultrasound confirmed a left renal stone 5 cm in diameter. Panendoscopy showed a normal urethra and bladder with normal ureteric orifices. A 4F ureteric catheter was easily passed up to 20 cm in the left ureter. X-ray showed a normal left ureter with a narrowed pelviureteric junction and a stone in the renal pelvis (Fig.).



Through a subcostal incision the left kidney was explored, the renal relvis was opened and the stone easily extracted. A classical Anderson-Hynes pyeloplasty was performed. The stent was removed on the fourth postoperative day and the nephrostomy tube on the seventh. The patient was discharged 3 days later in good condition.

Requests for reprints to: F. Ibrahim, Department of Urology, Khartoum Teaching Hospital, P.O. Box 384, Khartoum, Sudan.

Primary Amyloidosis of the Bladder

ROSALIND J. BUTTERWORTH and A. J. L. HART,
Department of Urology, East Glamorgan Hospital, Pontypridd

Case Report

A 77-year-old, previously fit lady presented with an 11-month history of intermittent dysuria, urgency, haematuria and occasional incontinence. Examination was normal apart from a blood pressure of 170/108 mmHG. FBC was normal; urea was 8.2 mmol/l and creatinine 167 μmol/l.

An intravenous urogram (Fig. 1) showed irregularity of the left wall of the bladder and an obstructed left upper urinary tract. At cystoscopy there was a lesion, thought to be a carcinoma, occupying the left wall and trigone. CT scan and examination under anaesthesia showed a large mobile mass in the bladder (Fig. 2).

Histology showed deposits of amyloid in the lamina propria with no evidence of neoplasia.

Bence Jones protein assay, serum electrophoresis, rheumatoid factor, chest radiography and rectal biopsy showed no evidence of systemic amyloid.

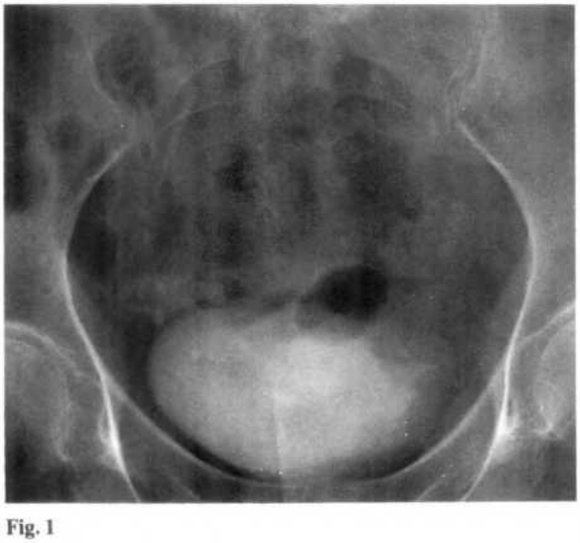


Fig. 1

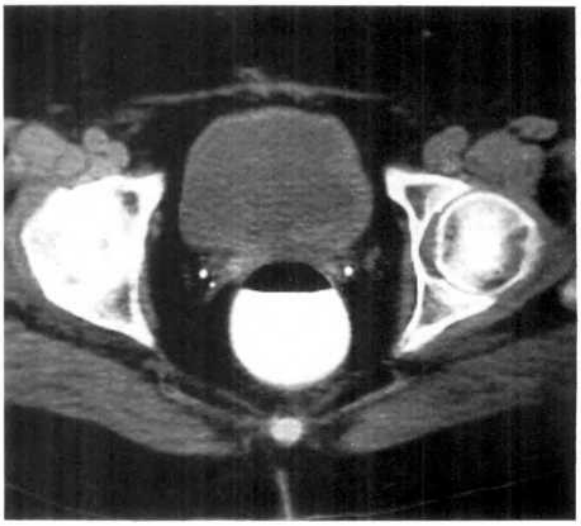


Fig. 2

Because of her age and lack of subsequent symptoms she has been treated conservatively.

Comment

Only 50 cases of amyloidosis of the bladder have been reported. Primary amyloidosis appears more common than secondary disease. Investigation to exclude systemic disease is mandatory.

The prognosis of the localised lesion appears good, whether treated by fulguration or local resection (Malek *et al.*, 1971; Mead *et al.*, 1982). Prognosis in the presence of systemic disease is poor, irrespective of treatment, especially if the patient presents with haematuria (Abramovici *et al.*, 1977).

Acknowledgement

We are grateful to Dr D. Stock, Department of Pathology, East Glamorgan Hospital.

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Requests for reprints to: A. J. L. Hart, Department of Urology, East Glamorgan General Hospital, Church Village, Near Pontypridd, Mid Glamorgan CF38 1AB.

Torsion of the Vas Aberrans

J. S. VIRDI, W. CONWAY and D. G. KELLY, *Department of Urology, St Vincent's Hospital, Dublin, Ireland*

Case Report

Torsion of the vas aberrans is rare and only 4 cases have been reported (Randall, 1939; Cywes, 1966; Ballastros Sampol *et al.*, 1986). We report 2 further cases.

Case 1. A 12-year-old boy was admitted with a 3-h history of an acutely painful right scrotum. On clinical examination the scrotum was swollen and extremely tender. Immediate surgical exploration was carried out through the mid-line scrotal raphe. An elongated sausage-shaped translucent cyst measuring 7 × 1.5 × 1.5 cm was found to be twisted (360°) on a long mesentery attached to the mid-portion of the groove between a normal testis and epididymis (Figs 1 and 2). The cyst was excised after ligation of the mesentery.

Case 2. An 18-year-old boy was admitted with a 4-h history of an acutely painful right scrotum. Six months previously he had had a similar pain which had lasted for 2 h. The scrotum was swollen and tender. Surgical exploration revealed a sausage-shaped cystic swelling measuring 5 × 2 × 2 cm twisted on a mesentery which was attached to the mid-portion of the groove between a normal testis and epididymis. The cyst was excised.

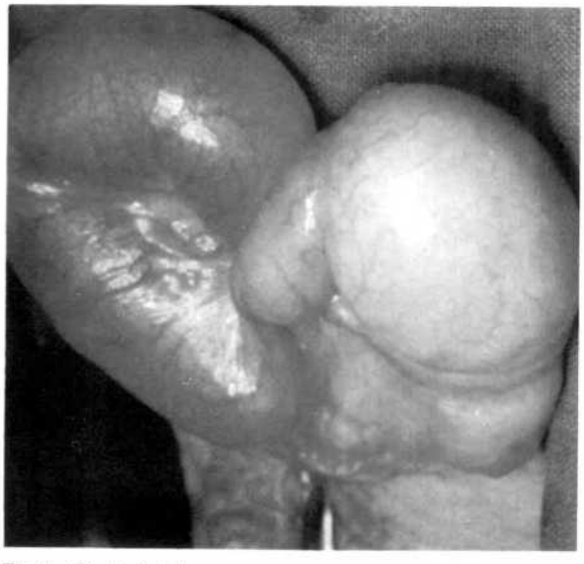

Fig. 1 Cyst twisted on mesentery.

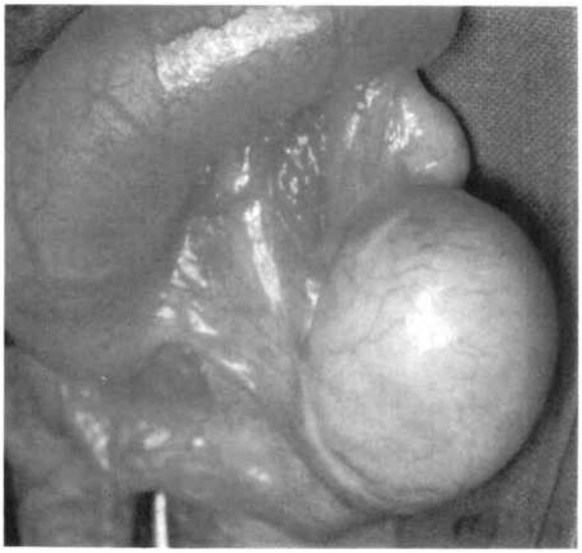

Fig. 2 Cyst with untwisted mesentery.

Exploration of the opposite scrotum in both cases revealed no abnormalities. Ultrasound scan of the renal tract was also normal. Histological examination showed the cyst to be filled with a milky fluid. The wall consisted of an outer layer of connective tissue lined by columnar ciliated and focally pseudo-stratified epithelium.

Comment

The vas aberrans (Organ of Heller: cranial and caudal aberrant ductules) is represented by a group of wolffian tubules usually associated with the floor of the groove between the testis and body of the epididymis. The histological appearance and tissue of origin are not clear-cut (Mostofi and Price, 1973). When presented as a torsion it is difficult to differentiate from torsion of the testis and immediate surgical exploration and excision are advisable.

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Requests for reprints to: J. S. Virdi, Department of Urology, St Vincent's Hospital, Elm Park, Dublin 4, Ireland.

Complete Prolapse of the Urinary Bladder

Y. T. CHAN, W. D. NG, T. F. YIN and T. F. KWOK, *Surgical B Unit, Princess Margaret Hospital, Hong Kong*

Complete eversion and prolapse of the urinary bladder, as distinct from mucosal prolapse, is a rarity. Only 4 well documented cases have been reported (Fish, 1961; Campbell, 1963; Cebeci and Sozer, 1968; Underhill and Altaffer, 1983). Ours represents the third case occurring in an adult and the first one successfully corrected by a definitive operation.

Case Report

A destitute, multiparous 84-year-old woman had a 5-year history of a mass in the genital area. She took little notice of it as it was asymptomatic, until one day a sudden attack of vaginal bleeding and suprapubic pain prompted her admission. Apart from occasional wetting of pants, there was no definite total incontinence. On admission, the creatinine was 1380 μmol/l.

Examination under anaesthesia revealed that the mass was covered by bladder mucosa with the trigone and ureteric orifices clearly exposed (Fig.). Reduction was unsuccessful. Instead, both ureters were catheterised. The creatinine dropped to normal following a few days' drainage. Intravenous venography showed bilateral hydronephrosis and apparent low insertion of ureters.

One month later, through a suprapubic approach, the everted bladder was reduced. The urethra was so widened as to admit one finger readily. A Marshall-Marchetti procedure was performed.

Convalescence was uneventful. She proved continent upon removal of the urethral catheter. However, subsequently she became bedridden and developed bed sores. A Foley catheter was reinserted and left indwelling until she died of senility 4 months later.

Comment

Because of the extreme paucity of information, the

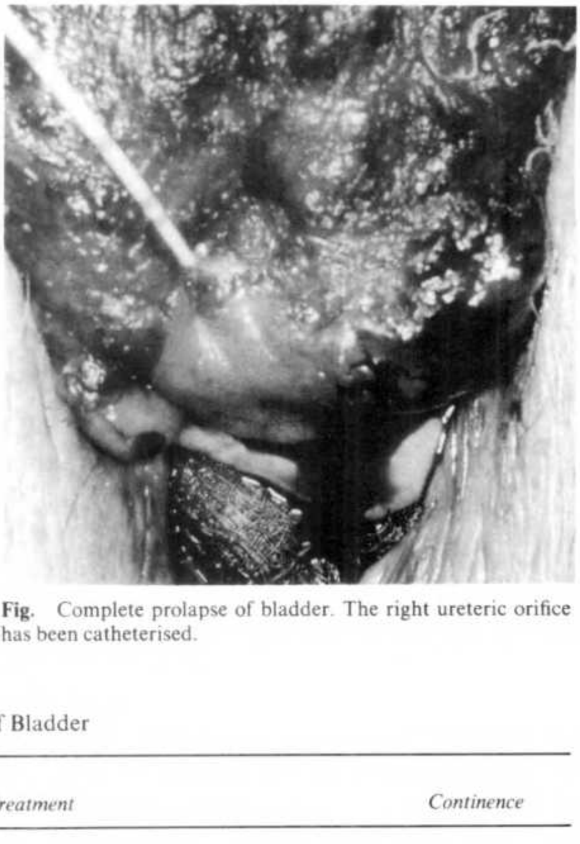

Fig. Complete prolapse of bladder. The right ureteric orifice has been catheterised.

Table Analysis of Reported Cases of Complete Prolapse of Bladder

Author	*Sex/Age*	*Predisposing condition(s)*	*Treatment*	*Continence*
Fish (1961)	F/17 months	Complete epispadias		
Campbell (1963)	F/2 years	Cough	Gentle squeezing and indwelling catheter	Not mentioned
Cebeci and Sozer (1968)	F/34 years	Nil	Suprapubic cystostomy, cystopexy and indwelling catheter	Not mentioned
Underhill and Altaffer (1983)	F/82 years	Pelvic injury, uterine prolapse	(1) Ureteric catheter drainage and vaginal reposition (2) Reduction and suturing of dome of bladder to rectus fascia (3) Anterior and posterior colporrhaphy	Totally incontinent
Present study	F/84 years	Multiparity, uterine prolapse	(1) Ureteric catheter drainage (2) Suprapubic reduction and Marshall-Marchetti operation	Continent

pathology and treatment of this condition remain speculative. Inordinate laxity of the vesical outlet and urethra is assumed to be the underlying mechanism, while a few predisposing conditions are identified (Table).

Treatment is aimed at reduction, prevention of recurrence and maintenance of continence. A suprapubic approach was required for reduction in all 3 adult cases, whereas prevention of recurrence and maintenance of continence was achieved by strengthening the bladder neck support, increasing urethral resistance and restoring the vesicourethral angle. We elected to perform a Marshall-Marchetti procedure on the premise that elevation and fixation of the vesical neck are major factors in the maintenance of urinary control, which can most effectively be accomplished by a retropubic repositioning operation, readily incorporated into the suprapubic reduction procedure. Anterior colporrhaphy, employed by Underhill and Altaffer (1983), proved inefficient in maintaining continence.

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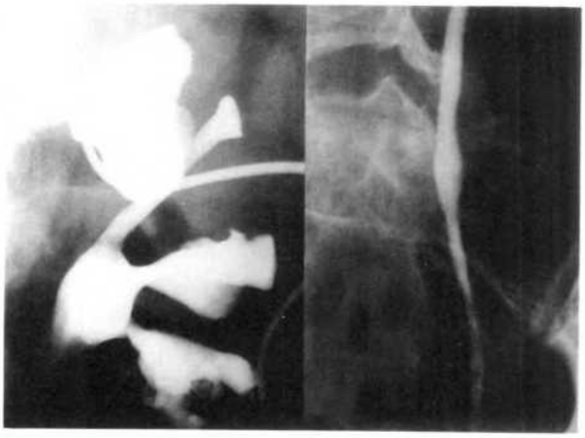
Requests for reprints to: Y. T. Chan, Surgical B Unit, Princess Margaret Hospital, Kowloon, Hong Kong.

Pelvic Irradiation, the Ureter and Extracorporeal Shockwave Lithotripsy

J. P. KELLEHER and M. E. SNELL, *Department of Urology, St Mary's Hospital, London*

Case Report

A 58-year-old lady was admitted for extracorporeal shockwave lithotripsy (ESWL) to a 2.5-cm, triangular-shaped stone in the lower pole calix of her left kidney; 22 years previously she had had a combination of external beam and intracavity irradiation for a stage 1 squamous cell carcinoma of the cervix, following which there was no recurrence. A 6F 24-cm ureteric stent sited prior to ESWL was noted to be "tight fitting". Following 3 treatments on the Dornier lithotriptor the bulk of the stone was still *in situ* and there had been only minimal fragmentation. A subsequent attempt at percutaneous nephrolithotomy was abandoned because of marked haemorrhage on forming the nephrostomy tract.



Several fragments of the stone moved into the renal pelvis and ureter, the most distal of which became lodged at the level of the pelvic brim. The subsequent obstruction was then relieved by the insertion of a percutaneous nephrostomy but this procedure was not followed by spontaneous passage of the stones (Fig.). Ureteroscopy was then attempted to retrieve the ureteric fragments but owing to the rigidity and limited calibre of the ureter the instrument could not be passed to the level of the stones. Even though the ureters had appeared normal on urography, the lower third of the left ureter was aperistaltic and narrow on antegrade ureterography. The calculi in the ureter and renal pelvis were then removed by open surgery.

Comment

The true incidence of ureteric damage following pelvic irradiation is unknown, but that as demonstrated by upper urinary tract dilatation on urography is very low (Underwood *et al.*, 1977). However, as shown here, ureters may be undilated on urography and yet be aperistaltic. In view of the complications that may follow if there is arrest of stone fragments above an aperistaltic segment of ureter, it would be prudent for patients who have had pelvic irradiation and are to have ESWL to be offered a preliminary assessment of ureteric peristalsis. This can be done in a non-invasive way by either radionuclide imaging or high dose fluoroscopy (Lewis *et al.*, 1989).

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Underwood, P. B. R., Lutz, M. H. and Smoak, D. L. (1977). Ureteral injury following irradiation therapy for carcinoma of the cervix. *Obstet. Gynecol.*, **49**, 663–669.

Requests for reprints to: J. P. Kelleher, Department of Urology, St Mary's Hospital, Praed Street, London W2 1NY.

British Journal of Urology (1990), **66**, 438–442

0007–1331/90/0066–0438/$10.00

Points of Technique

Minimisation of Stone Deflection during Extracorporeal Shockwave Lithotripsy Monotherapy for Ureteric Calculi *in situ*

J. A. THORNHILL, K. MORAN, S. SHEEHAN, J. SMITH and J. M. FITZPATRICK, *Department of Surgery, Mater Misericordiae Hospital, Dublin, Ireland*

X-ray guided extracorporeal shockwave lithotripsy (ESWL) monotherapy using the Siemens Lithosar is a highly effective means of treating ureteric calculi *in situ* (Thornhill *et al.*, 1989). In this unit all ureteric calculi are treated in this manner except for those overlying the posterior bony pelvis, which are managed primarily by endoscopic methods.

We have observed in using this machine that a proportion of ureteric calculi are not initially amenable to ESWL *in situ* because raising the shockhead into the treatment position causes anterior deflection of the stone beyond the limits of machine focusing adjustment. This occurs because the shockhead lies against the spine when treating ureteric calculi. Elevating the shockhead has the effect of pushing the vertebral column, and therefore also the ureter plus stone, away from the lithotriptor. This problem does not arise when treating renal calculi because they lie posterolaterally and the kidney is surrounded by compressible soft tissue.

We have overcome this problem by securing the patient to the lithotriptor with a compression abdominal strapping (Fig. 1). This greatly reduces stone deflection to within the limits of machine adjustment and ESWL can then proceed (Fig. 2). This modification has enabled treatment in 9 patients for whom ESWL would previously have

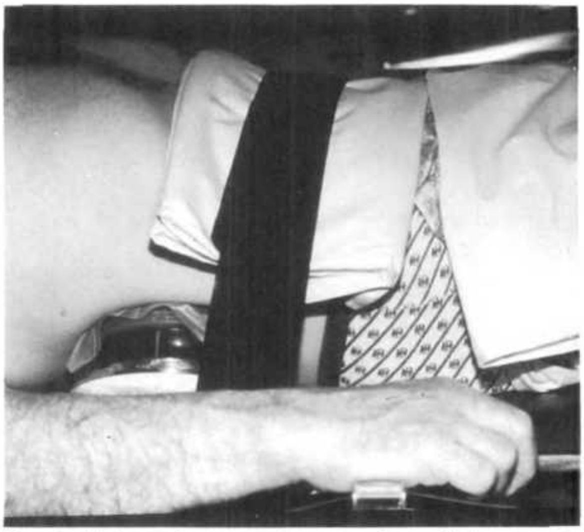
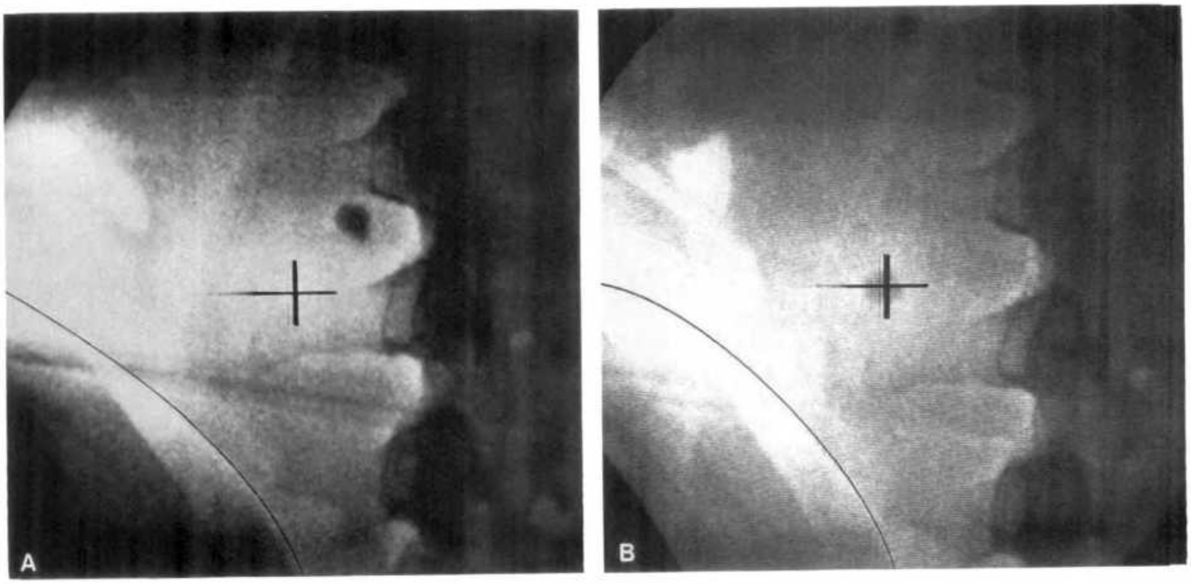


Fig. 1 Abdominal compression strapping which prevents anterior deflection by the treatment head.

Fig. 2(A) X-ray localisation imaging shows the ureteric calculus deflected beyond the limits of machine adjustment by the treatment head (bottom left). (B) with abdominal compression strapping the stone can be targeted for lithotripsy.



been abandoned because of failure of localisation. Fragmentation was seen in each patient, including 3 upper ureteric calculi, 3 mid-ureteric and 3 lower ureteric calculi (mean stone diameter 0.8 cm).

Users of the Dornier Lithotriptor advocate ESWL in the prone position for stones situated anteriorly (Tiselius *et al.*, 1989) but this time-consuming approach involves turning the patient and totally relocalising the stone with the contralateral treatment head. We have been unable to achieve fragmentation using the Siemens machine in this manner, possibly because the shockwaves are dissipated by intervening bowel.

We therefore recommend abdominal compression strapping as a simple, cost-effective method for reducing ureteric stone deflection by the Lithostar treatment head. It may cause some discomfort requiring sedation or analgesia but it ensures that virtually all ureteric calculi can be treated successfully *in situ* by ESWL monotherapy.

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Requests for reprints to: J. M. Fitzpatrick, Department of Surgery, Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland.

Confirmation of Position of Double J Stent Inserted at Open Operation

S. GEPI-ATTEE, K. GANABATHI and J. C. GINGELL,
Department of Urology, Southmead Hospital, Bristol

Since the first description in its present form (Finney, 1978), the double J stent has become established as a means of internal drainage and splintage in surgery, trauma and obstruction of the renal pelvis and ureter (Pocock *et al.*, 1986). Notable to the contribution of the stent to open surgery of the ureter and pelvis is its distinct advantage over external drainage by a T-tube, reflected in a shorter hospital stay, effective drainage and reduction in infection (Sibley *et al.*, 1987). In any operation on the kidney or ureter requiring a stent it is necessary to ensure that the distal end of the stent is properly sited in the bladder and not in the lower ureter. In practical terms this means either confirmation by cystoscopy or radiological screening. Both procedures are time-consuming and interrupt the continuity of the operation. It is possible, however, to confirm that the lower end of the stent is in the bladder reliably, simply, inexpensively and without delay or disruption of the operation. The procedure is as follows:

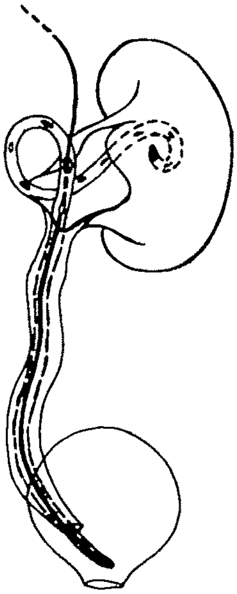

Fig. Diagram of antegrade insertion of double J stent at open operation.

1. Catheterise the patient before he or she is turned to the lateral position and empty the bladder.
2. Fill the bladder with 150 to 200 ml of a solution of 1% methylene blue in 500 ml normal saline and spigot the catheter.
3. Perform the operation and insert the double J stent antegradely (Fig.). As soon as the guide wire is removed methylene blue effluxes from the side holes of the stent and confirms that it is in the bladder. If the dye does not efflux directly, press gently on the suprapubic area. If the dye still does not appear, the stent is not in the bladder and insertion must be attempted again.
4. As soon as entry into the bladder is confirmed the urethral catheter should be unclamped and connected to closed drainage.
5. The position of the stent can be confirmed by standard X-ray in the post-operative period. We have found this method to be uniformly successful and because of its simplicity we recommend its wider use.

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Sibley, G. N. A., Graham, M. D., Smith, M. L. *et al.* (1987). Improving splintage technique in pyeloplasty. *Br. J. Urol.*, **60**, 489–491.

Requests for reprints to: J. C. Gingell, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

Withdrawal of Intraprostatic Coils

P. VANLEEUW, J. L. JORION and G. LEDENT, *Division of Urology, Department of Surgery, Clinique Sant-Pierre, Ottignies, Belgium*

Intraprostatic coils have been introduced as a palliative method to avoid indwelling catheters for inoperable patients with urinary retention due to benign prostatic hypertrophy (Fabian, 1980). Insertion of the device is usually easy, but sometimes the length may be inadequate or it may migrate toward the bladder, with secondary retention.

Unfortunately, withdrawal with forceps will result in elongation of the coil which then cannot be used again. We propose a simple and effective manoeuvre for withdrawing an intraprostatic coil (Urological Spiral*) without damaging it.

Under lignocaine gel local anaesthesia and fluoroscopic control, a 5 F Fogarty catheter is inserted through the spiral. When the radiopaque tip of the catheter is seen protruding 3 to 4 cm from the coil, the balloon is inflated with 1.5 ml contrast medium. Gentle traction on the catheter then permits easy positioning or extraction of the device (Fig. 1A).

Catheterisation of longer coils may sometimes be difficult. In such cases a 0.035 inch guide wire through a 6 F open-end ureteric catheter may be used in order to find the right way by manipulation

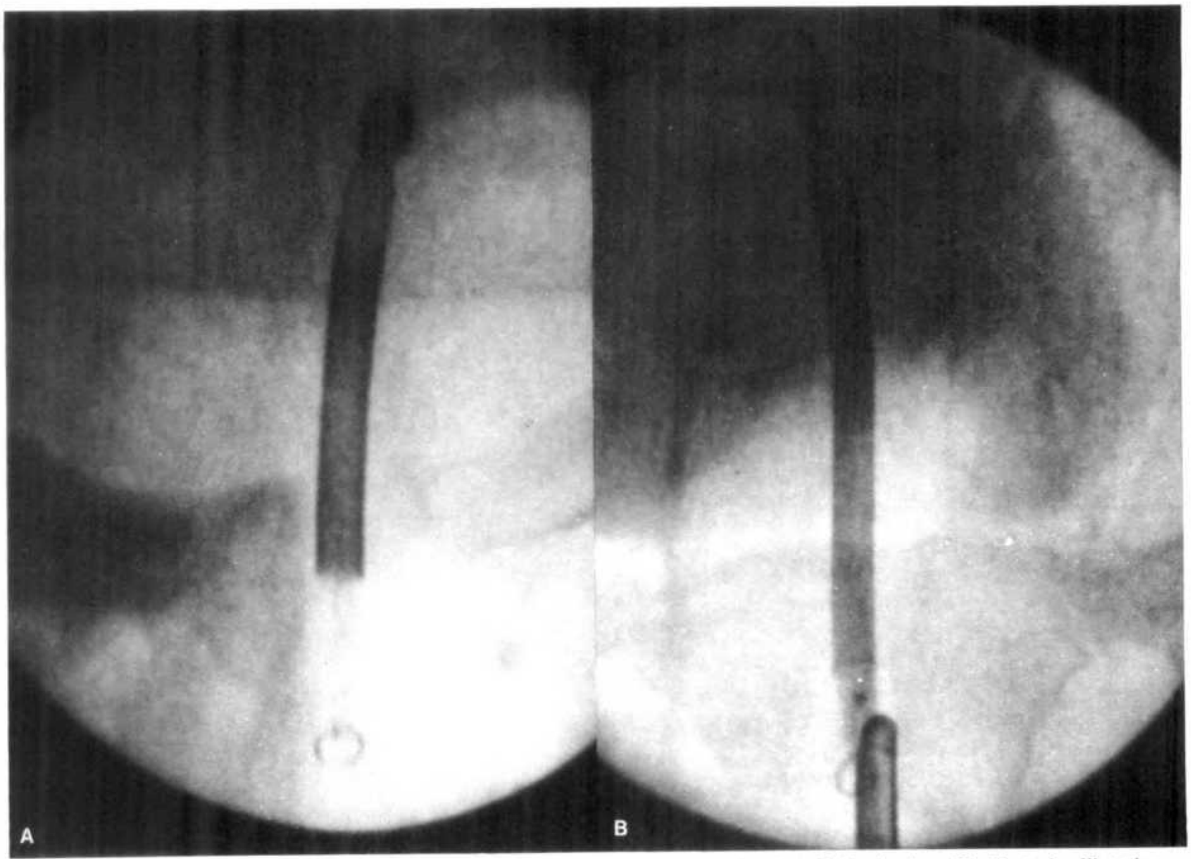

Fig. 1 (A) Fogarty catheter inflated in the bladder and withdrawn on the tip of the device. (B) Ureteric dilatation balloon inflated through the spiral.

of the guide wire under fluoroscopic control. A 10-mm dilatation balloon 12 cm in length is then inserted over the guide wire and inflated inside the device, which can be withdrawn (Fig. 1B).

It is important to ensure that the catheter passes through the sphincteric part (head) of the spiral. Otherwise, traction of the prostatic part (body) will result in kinking of the sphincteric over the prostatic part.

This simple technique will help to preserve many of these costly devices.

*Uromed Kurt Drews, Gewerbering 8, 2000 Oststeinbek, RFA).

Reference

Fabian, K. M. (1980). Der intraprostatische "Partielle Katheter" (Urologische Spirale). *Urologe A*, **19**, 236–238.

Request for reprints to: J. L. Jorion, Division of Urology, Clinique Saint-Pierre, Av. Reine Fabiola, 1340—Ottignies, Belgium.

Multiple Transverse Taeniamyotomy of the Caecum after Restorative Cystoprostatovesiculectomy for Bladder Cancer

E. ALCINI, M. PESCATORI, A. D'ADDESSI, F. GRASSETTI, G. ANASTASIO, M. GIUSTACCHINI and G. GRASSO, *Department of Surgery, Division of Urology, Catholic University of the Sacred Heart, Rome, Italy*

Bladder replacement using an intestinal segment is becoming the procedure of choice after cystoprostatovesiculectomy for cancer. Our experience with both an intact and a detubularised intestinal tract has already been reported (Alcini *et al.*, 1985a, b, 1989). We now describe surgical technique, transverse taeniamyotomy, which increases the capacity and decreases the resistance and motility of an intact ileocaecal bladder.

Multiple transverse incisions are carried out on the antimesenteric taenia of the disconnected ileocaecal tract, saving the caecal mucosa (Figs 1 and 2), and also on the mesenteric tract. The compliance of the ileocaecal tract is recorded both before and after taeniamyotomy, using a probe connected to a closed air-filled system with high compliance which we constructed ourselves. The inflatable balloon of the probe is inserted into the caecum through the ileum and the ileocaecal tract is then inflated with air.

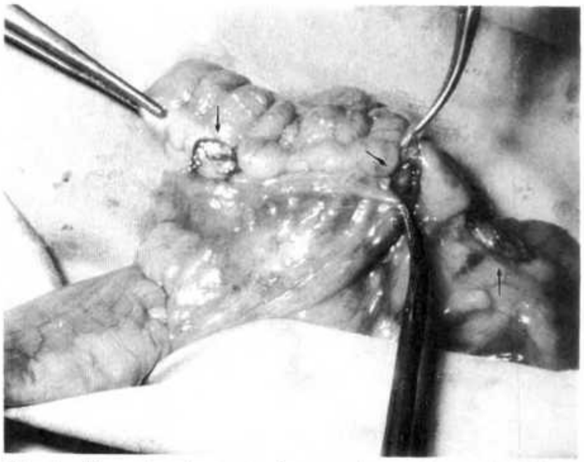

Fig. 1 Three taeniamyotomies are shown (arrows). Where myotomy has not yet been performed the calibre of the caecum is clearly smaller.

The ileocaecal tract is subjected to progressive insufflations up to 180 ml both before and after taeniamyotomy and the intraluminal pressures for similar filling volumes are noted (Fig. 3). The number of myotomies varies between 3 and 6.

Division of the muscular coat leads to an increased intraluminal radius and accordingly to a decreased intraluminal pressure.

In the 15 patients treated by this method we observed a satisfactory interval between each micturition, *i.e.* approximately 2 h at night and 3 to 4 h during the day, with continence. These functional advantages over other techniques are mainly evident during the first year after surgery. The intervals between each micturition tend to increase to 4 to 5 h after 1 year, due to intestinal adaptation and physiological enlargement of the new bladder (Fig. 4).

This procedure is simple, safe and effective after cystectomy and achieves good clinical and functional results.

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Requests for reprints to: E. Alcini, Department of Surgery, Division of Urology, Catholic University of the Sacred Heart, Rome, Italy.

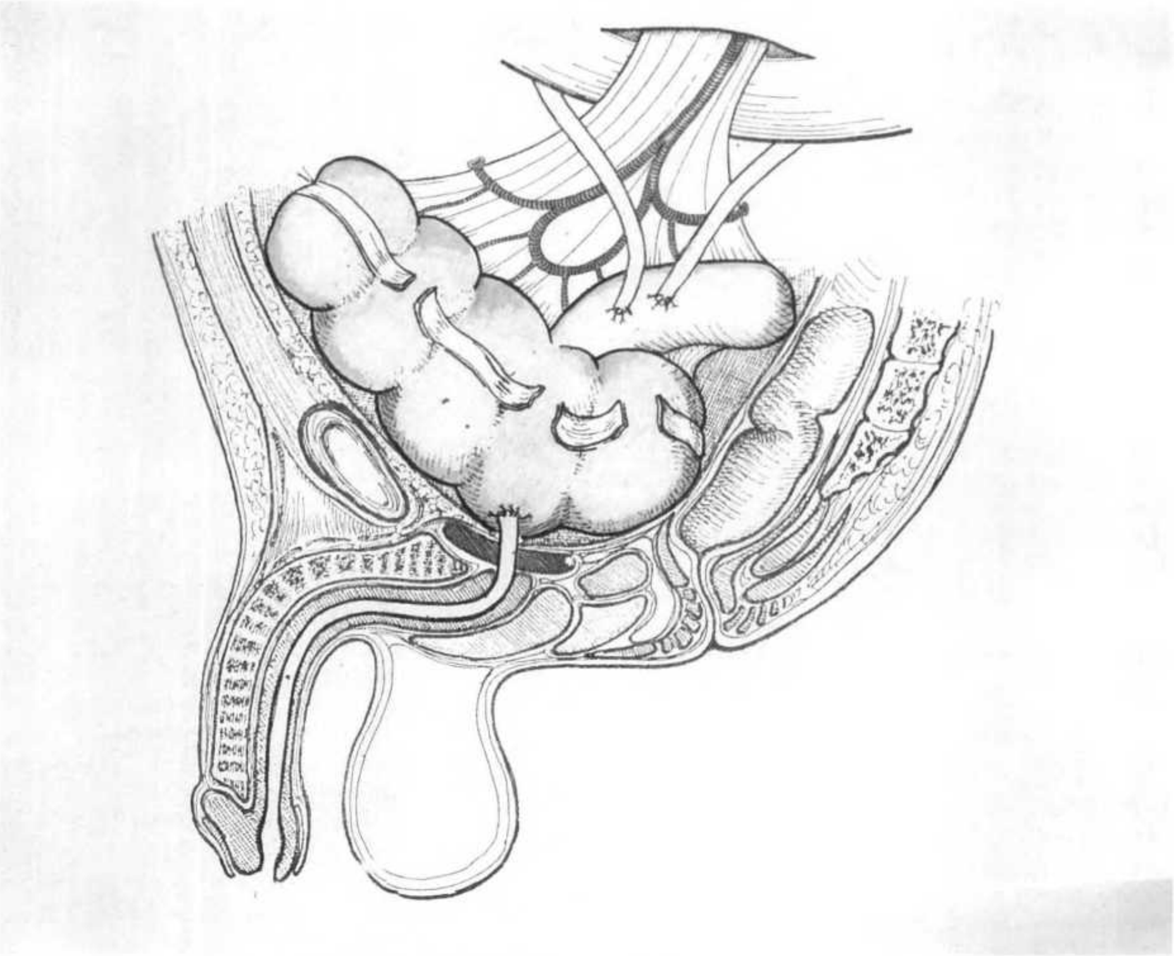

Fig. 2 Final view of ileocaecourethrostomy with multiple caecal taeniamyotomies.

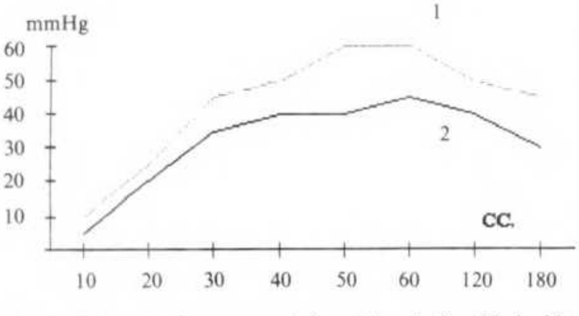

Fig. 3 Pressure/volume curve before (1) and after (2) double taeniamyotomy.

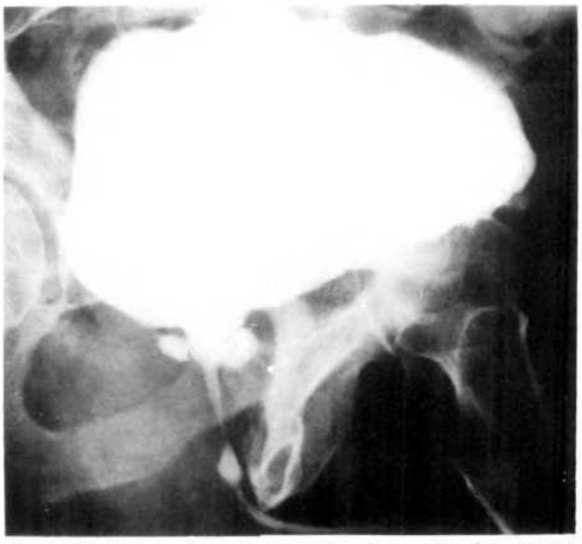

Fig. 4 Voiding cystography in patient 2 months after surgery shows satisfactory bladder compliance.

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Correspondence

Dear Sir,

re **Bladder outflow tract obstruction and urinary retention from benign prostatic hypertrophy treated by balloon dilatation.** K. P. Gill *et al. Br. J. Urol.*, **64**, 618–622, 1989.

Gill *et al.* document failure of balloon dilatation to improve the symptoms or urodynamics in obstructed patients. The paper underscores several important points regarding balloon dilatation.

First, in order to be effective, the entire prostate must be dilated. Reference to Figure 2 demonstrates that at least 50% of the length of the gland, the apical portion, is not being stretched. This may be analogous to resection of only the bladder neck during TURP, *i.e.* very unlikely to be rewarding. Second, in order to be effective, the prostate must be effectively dilated. The absence of any cystoscopic or urethrographic evidence of a urethral split (commissurotomy) suggests that nothing was accomplished. While the split *per se* may not be the mechanism of action of dilatation, its absence can be taken as a sign that nothing really happened. Third, in order to be effective, the prostate must be dilated significantly. The mean prostatic volume in this series was about 69 ml. Computing the solid geometric dimensions (assuming the prostate to be roughly cylindrical) reveals that the maximal volume effectively dilated by a 25 ml balloon would be about 30 ml, allowing for some compression of the adenoma between the capsule and the balloon. Large glands would not be expected to respond. Fourth, there is the question of the placebo effect of sham procedures. If it is indeed true that these prostates were in fact not dilated, then the authors have established that the placebo effect of balloon dilatation is about 11% and that raises the question of why the placebo effect of dilatation is less than the placebo effect of medications.

Yours faithfully,

L. Klein
Division of Urology, Scripps Clinic Medical Group, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA.

Reply by Gordon Williams. Unfortunately, Dr Klein cites no evidence to support his statement that the entire prostate must be dilated for balloon dilatation to be effective. There is always a tendency with such a technique for the balloon to rise up into the bladder, as shown in Figure 2 of our paper. With regular screening, the balloon is re-positioned to ensure that the full length of the prostate is dilated. Dr Klein's suggestion that only 50% of the prostate has been dilated does not take account of the magnification shown on the X-ray. In this study, and in our more recent study (J. McLoughlin *et al.* (1990). *Br. J. Urol.* In press), where we have used a purpose-built 35 mm balloon positioned endoscopically to ensure full prostatic dilatation, there has been no relationship between urethral splitting and success or failure. In the study referred to by Dr Klein the urethra was split in 25 patients and only 1 of them was unobstructed urodynamically. As a result of such poor correlation we have now given up looking to see whether or not the urethra has been split as it is totally irrelevant to the outcome of balloon dilatation. In our recent study we have again shown no correlation with prostate size, although we have shown a 50% objective short-term improvement. This is lost by 6 months. In studies on non-operative treatment of benign prostatic hypertrophy where a placebo has been used, they usually cite a placebo effect of around 30%. This study, with only 11% of the patients showing objective evidence of improvement, suggests that there is no placebo effect but confirms our original conclusion that balloon dilatation up to 25 mm is an inadequate treatment for patients with bladder outflow obstruction when assessed objectively.

Dear Sir,

re **Circumcision—which dressing?** D. C. S. Gough and Nora Lawton. *Br. J. Urol.*, **65**, 418–419, 1990.

I read with interest David Gough's paper on circumcision dressings. We too have had problems finding a suitable dressing for the penis after circumcision and have now abandoned any form of "wrap around" dressing in favour of the following method. After the procedure, the urethral meatus, glans and coronal sulcus are smeared liberally with the jelly scraped from the paper covering a square of Soframycin impregnated with tulle gras. A Melolin square, with the plastic side inwards, is then taped to the suprapubic area to form an apron covering the penis and scrotum. This keeps the child's pyjamas or bed clothes away from the circumcision site.

Yours faithfully,

W. Richmond
Department of Urology, Royal Albert Edward Infirmary, Wigan WN1 2NN.

British Journal of Urology (1990), 66, 444

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Glasgow. 25–28 June 1991

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 4 January 1991.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology (1990), **66**, 445–447

Diary

1990

October 25–26	Urological Management of Spinal Injury, Institute of Urology, London. Contact: Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
October 25–29	Second International Congress on "The Pelvic Floor"—Update Management. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.
November 7	Platelets and Endothelium in Renal Disease-Workshop. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115
November 8–9	Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
November 10	Basic Science and Urology Symposium, Glasgow. Contact Mr R Scott, Department of Urology, Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ER.
November 16	Urology for General Practitioners. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.

1991

January 4	Final date for submission of abstracts for 1991 BAUS Annual Meeting.
January 14–February 1	Short Courses in Urology and Nephrology including: Disorders of Bladder Function, Reconstructive Surgery, Disorders of the Female Urinary Tract, Urological Trauma and Emergencies, Acute and Chronic Renal Failure, Transplantation, Management of Stones and Upper Tract Obstruction, Endoscopic Urology and Recent Technological Advances in Urology, The Retroperitoneum, Surgical Techniques, Urological Problems in the Elderly. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
January 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
February 3–6	International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
February 7–8	Uro-Radiology '91. For further details of this course please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
February 23–March 2	Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ.

March 11–15	Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
March 16–17	International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
April 8–28	Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
April 12–13	Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France.
June 2–6	American Urological Association, Metro Toronto Convention Centre, Toronto, Canada.
June 7–8	Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09.
June 16–20	Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 17–22	Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
June 25–28	BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
July 2–3	Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.
September 16–19	Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.

1992

January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

1993

May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 13–17	Canadian Urological Association Annual Meeting, Toronto. Contact: Dr R. B. Auld, Suite 620, 5991 Spring, Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

1994

May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

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Book Reviews

Urinary Tract Inflammation and Infection. By J. E. Fowler, Jr. Pp. xiii+339. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price: £55.50.

This book can be recommended as the standard text on urinary tract infection for the practising clinician and it provides comprehensive references on all aspects of related disorders. Most of the chapters are written by a urologist and his approach is very much in accord with that of his British counterparts, it is refreshing to note that he does not find much merit in radiographic and endoscopic investigations of the urinary tract in the female with the occasional bout of bacteriuria

The major merit of this book is its logical thinking and the inculcation of good habits. Since there have been no innovative techniques or programmes to report, we are going to have to wait for some advances in immunology, taking us beyond microbiology, before we start marching forward again. There is no new information available to help us answer the problem questions which have plagued us for decades, namely, interstitial cystitis, non-bacterial prostatitis and the urethral syndrome. At £55.50, this volume of just over 300 pages does seem a bit expensive.

Extracorporeal Shock Wave Lithotripsy. Medical, Technical, Economic and Policy Implications (Health Service Studies 2). Edited by P. Carlsson and H.-G. Tiselius. Pp. 128. Linkoping: Linkoping Collaborating Centre. 1989. Price: US $25.00.

This is the second Health Service Study book published by the Linkoping Collaborating Centre in association with the World Health Organisation. The book comprises reports of presentations to a conference on ESWL held in November 1988 The book is divided into sections relating to medical, evaluation, technical, organisational and policy aspects of ESWL.

The early chapters are devoted to reports of experience from a number of centres with ESWL using different machines. Most of the information presented is a repetition of material available elsewhere. There is an interesting report of a comparison of ESWL and percutaneous nephrolithotomy. This was not a randomised study but a comparison of patients managed in different centres. The cost per successfully treated (stone-free) patient was higher for ESWL than for PCNL in all categories of renal calculi, and this was especially so for large calculi The complication rate after PCNL was, however, higher than after ESWL. The author's conclusion was that ESWL should be the first choice for ureteric and renal calculi to up to a diameter of 2 to 3 cm, but larger calculi may be more effectively and less expensively treated with PCNL or a combination of PCNL and ESWL.

British urologists receive some criticism for not grasping the nettle of randomised controlled clinical trials of ESWL when it was first introduced. Part of the problem with technology assessment is that the technology is changing constantly. It would be hard to argue now for a study comparing a 40-minute, anaesthesia-free out-patient treatment with a percutaneous approach to a small calculus in the upper calix.

Although already slightly dated, this small book contains some useful information, particularly for those considering buying a lithotriptor. The book contains, for example, reports on experience with mobile lithotripsy services which may be relevant to some parts of the United Kingdom. Doubtless this book does not contain the last word on the health economy debate!

Urological Pathology. Edited by W. M. Murphy. Pp. x+603. Philadelphia: Saunders. 1989. Price: £78.00.

Textbooks of urological pathology were, until very recently, conspicuous by their absence. Now 3 texts have appeared, all covering the same topics—Petersen's *Urologic Pathology* (1986), Gary Hill's 2-volume *Uropathology* (1989) and, most recently, *Urological Pathology*, edited by W. M. Murphy.

The book under review has 13 contributors and all of the important topics are well covered, including, as is customary with North American texts, the adrenal glands. The book is lavishly illustrated with black and white photographs and there are also colour photographs. In general the illustrations are excellent and only a few fall short of the highest standards. The contributors are experts in their fields and the work is both authoritative and comprehensive.

The immediate comparison is with Hill's 2-volume work, which is more than twice the price (and size). There are some subjects in Murphy's book which are not dealt with in such depth as in Hill's, but as a reliable, up-to-date text it represents very good value.

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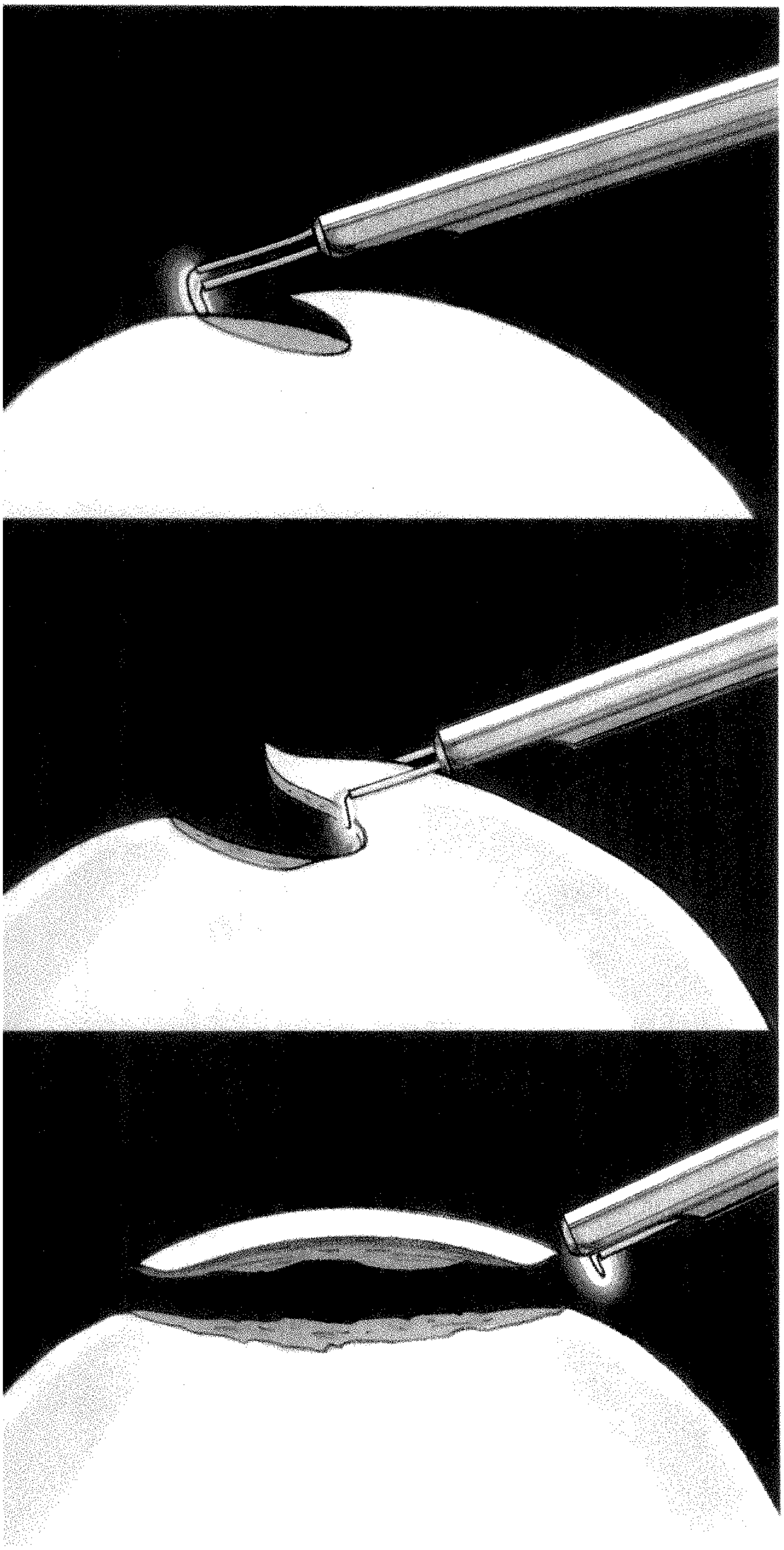

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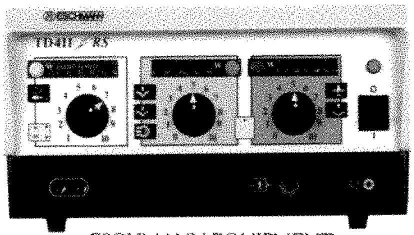

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REVIEW

Prostatectomy—an Open or Closed Case

D. E. NEAL

Department of Urology, Freeman Hospital, Newcastle upon Tyne

"Urologists are a quiet unassuming group proud of their role in the development of endoscopic surgery. It takes more than a few stones to ripple their pond, but a boulder has just rolled in."; so ran a recent editorial in the Lancet (1989). The origin was a retrospective study of 54,000 prostatectomies which found an increased risk of death 90 days, 1, 5 and 8 years after transurethral prostatectomy (TURP) compared with open operation (Roos *et al.*, 1989): the old sore was reopened.

The study is all the more disquieting because it followed reports from the same group showing that after 8 years the chance of a second TURP was triple that of open operation (Roos and Ramsay, 1987; Wennberg *et al.*, 1987) and that after TURP persistent urological problems were commonplace (Fowler *et al.*, 1988), resulting in little improvement in the quality of life. At first sight, these reports appear to be sending a clear message—perform more open prostatectomies—but the issues at the heart of these studies are complex and merit a reflective approach. Transurethral prostatectomy has served urology steadfastly, demonstrating clearly the need for specialist training and signalling vigorously the benefits of an increased number of urologists. Have we been hoist with our own petard?

There are 4 main matters to be considered when comparing open prostatectomy and TURP. These are the early death rate and morbidity, the late death rate and morbidity, the symptomatic outcome and the rate of reoperation. We have to decide whether to include only the best results or whether all centres and all surgeons should be weighed in the balance. A further confounding factor is the indication for operation.

Early Mortality After Prostatectomy

In the early part of the century, only men with retention, infection, stone formation or renal impairment underwent prostatectomy. Even in the 1930s, mortality at many hospitals remained at 20%, but in expert hands was about 5 to 6%. More recently, the early mortality rate of open prostatectomy averaged 2.5% (Turner and Belt, 1957; O'Connor *et al.*, 1963; Beck and Gaudin, 1970). The best mortality rate of open prostatectomy is now probably about 1%.

In the mid 1970s, TURP was performed in 80% of men in specialist units and by the mid 1980s this figure had increased to 95% (Melchior *et al.*, 1974; Chilton *et al.*, 1978; Wennberg *et al.*, 1988; Neal *et al.*, 1989). There seems little doubt that the inpatient mortality rate of TURP, averaging about 1.6% (Bergman *et al.*, 1955; Holtgrewe and Valk, 1962; Melchior *et al.*, 1974; Chilton *et al.*, 1978), was lower by about 1% than that of open prostatectomy. It is therefore necessary to keep in perspective recent findings of a small excess late mortality after TURP compared with open prostatectomy (Roos *et al.*, 1989). In over 3000 men undergoing TURP for clinically benign disease in 13 selected North American urological clinics in 1987, death was a rarity, occurring in only 0.1% (Mebust *et al.*, 1989).

Several studies have reported no difference in 90-day mortality between the 2 operations (Roos and Ramsay, 1987). It should be noted that after either type of prostatectomy an equal number of men die in the second or third months after operation as they do in the first. This finding of increased mortality should receive further attention.

Risk of death after open prostatectomy and TURP

When contrasting the results of TURP and open prostatectomy, it will be recalled that the 2

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procedures are neither truly comparable nor interchangeable. Open operations are generally performed on large glands and when TURP is performed on these larger glands, there is an increased resection time and increased post-operative morbidity (Bergman *et al.*, 1955; Melchior *et al.*, 1974; Mebust *et al.*, 1989), perhaps because the very large gland is more common in the older man (Berry *et al.*, 1984).

It is only too easy to be over-optimistic over the duration of anaesthesia required for TURP: several authors have reported in large series that the amount of tissue resected averaged 25 g and that the mean duration of anaesthesia was 1 h (Melchior *et al.*, 1974; Meyhoff, 1987). We do not, in all honesty, know the relative safety, or indeed the relative merit, of open prostatectomy and TURP for the larger gland, but it seems likely that they have similar risks—given a surgeon skilled in both. It is a tribute to the tenacity and eloquence of the dedicated resectionist that it is necessary to recollect that open prostatectomy still has a role in the management of outflow obstruction. Indeed, the open operation may be better for the fitter younger man with a large prostate, particularly in view of the greater risk of repeat operation after TURP (see below).

Risk factors for early morbidity and mortality

These include renal impairment, urinary infection (Melchior *et al.*, 1974), emergency admission, retention, age, medical problems and an inexperienced surgeon (Holtgrewe and Valk, 1962). Elderly men in the highest risk category have an early death rate of 5 to 8%—more than 5 to 10 times greater than that of the remainder (Chilton *et al.*, 1978). Nevertheless, a recent large North American study (Mebust *et al.*, 1989) have shown that death rates can be kept low, even in this highest risk group.

Urologists must address carefully the question of morbidity after prostatectomy in the years ahead because the average age of the population is increasing. Whilst unexpected death or morbidity after prostatectomy is usually credited to cardiovascular disease, the prudent urologist is aware that the cardiovascular system and kidneys of elderly patients do not tolerate the often combined physiological insults of hypovolaemia, hypoxia, sepsis and hypothermia which so easily accompany prostatectomy if the surgeon or anaesthetist should fail the patient. Decreases in cardiac output of about 17% and blood volume of about 12% have been reported during TURP (Mebust *et al.*, 1970); there is scope for further study in this area. On the other hand, TURP is free from wound infection and vesicocutaneous fistulae, though rectoprostatic fistulae may occur due to technical error after either procedure.

Sepsis is a factor whose ill-effects the urologist can diminish. The prompt diagnosis and adequate treatment of urinary infection is often difficult in urological units, where patient turnover is high and men are admitted the day before surgery and then discharged the day after catheter removal. Only too often, urinary infection is pursued and treated in a perfunctory manner, but careful antibiotic usage in treatment and prophylaxis may improve mortality and morbidity (Mebust *et al.*, 1989).

The early weeks after either type of prostatectomy may be an unhappy experience. One recent study found that within 3 months, 15% of men reported occasional difficulty in voiding owing to clots, 9% needed recatheterisation, 7% developed urinary infection lasting more than 2 weeks, 8% were readmitted to hospital and 24% visited a doctor because of a prostate problem (Fowler *et al.*, 1988).

Variation in outcome between different units

Death rates after prostatectomy in some centres may be double or quadruple what most urologists would consider acceptable (Wennberg *et al.*, 1987) and the recent Confidential Enquiry into Peri-Operative Deaths (Buck *et al.*, 1987) highlighted the need both for specialist surgeons and regular audit. Marked, unexplained variation in death rates, morbidity, duration of stay and rates of reoperation should receive careful attention. Several factors should persuade urologists of the need to administer clinical audit and to develop methods of diminishing unexplained variation between surgeons—quite apart from the obvious benefits to the patient and urologist. We should understand the effects which are likely to accrue from the recent transfer of litigation costs from the doctor to the health authority and from the pressing need to determine the outcome and costs of commonly performed operations. It is surely better to grasp firmly this nettle than to bequeath a web of pettifogging and pinching bureaucracy which others will fashion, only too eagerly, should we fail to act.

Late Mortality and Morbidity

Death in the long term after prostatectomy

Compared with age-matched controls, an excess death rate has been found in the long term in men undergoing prostatectomy, particularly in those with retention (Malone *et al.*, 1988; Roos *et al.*, 1989). The reasons remain obscure, for whilst myocardial infection is the commonest cause, the accuracy of the certification is uncertain. It is a potential concern that some deaths may be more closely related to the operation, perhaps being due to thrombo-embolic disease or urinary sepsis.

Death in the long term—TURP and open prostatectomy

The more surprising, and alarming, finding of these recent studies was that there appeared to be an excess risk of death 90 days, 1, 5 and 8 years after TURP compared with open operation. The relative risk of death from TURP ranged from 0.93 to 1.43, averaging 1.3 at 1 year, but the relative risk of myocardial infarction was 2.5 (Roos *et al.*, 1989). This tendency toward an increased risk of death after TURP was tentatively supported in the healthiest cohort (not in a nursing home, no cardiovascular disease, no drugs and a good physical status score). The relative risk of death after TURP in this cohort was 1.2 on univariate analysis and 1.6 on multivariate analysis, which was not statistically significant, but the increased risk of death from cardiovascular disease was confirmed.

The difference in late death rate between TURP and open prostatectomy (Roos *et al.*, 1989) was of the same magnitude as the difference in early post-operative mortality reported between different centres or different surgeons for any type of prostatectomy. Nearly 60% of men underwent open prostatectomy in Oxfordshire (studied over a 15-year period from 1963–1978), where the mortality rate of TURP and open prostatectomy at 90 days (3.7%) was more than double that in Manitoba (1.7%; a 15-year period from 1970–1985) and greater than that in Denmark (2.5%; an 8-year period from 1977–1985), where only 25% underwent open operation.

Over 65% of all prostatectomies (open plus TURP) in this series were performed in Denmark, where no difference was found in 90-day mortality between the 2 procedures; this was the contemporary series collected over 8 years. It will not have escaped notice that the region performing more than 50% of its operations by the open method had the greatest early mortality, an observation which would not induce most urologists to perform more open procedures. This is in keeping with previous studies which have found that an increased risk of death after TURP is confined to hospitals with an overall high mortality rate which tend to perform a relatively high proportion of open prostatectomies (Wennberg *et al.*, 1987). For the dilettante urologist, these studies provide no succour.

The idea that a TURP lasting 40 minutes could cause a fatal heart attack 8 years later is not easy to accept. Is it really possible that factors such as hypovolaemia, hypothermia, hypotension, glycine absorption, hyperammonaemia, hyponatraemia or sepsis could cause subtle metabolic disturbances leading to permanent cardiac damage? Do these results indicate a genuine long-term complication of TURP? Or is it more likely that these results are a consequence of patient selection? We do not know.

The authors grant that the deficiencies of a retrospective study precluded a satisfactory explanation of these findings and state that the increased risk may be a consequence of "unmeasured characteristics". This concession will strike a chord with many urologists, for the general condition of some elderly men renders an open operation undesirable, even if not wholly out of the question. Other unmeasured characteristics (Roos and Ramsay, 1987; Wennberg *et al.*, 1987; Roos *et al.*, 1989) included the size of the gland, the length of resection, the surgeon performing the operation and the presence of urinary retention, the latter being associated with increased early and late mortality (Malone *et al.*, 1988). It remains an open question, therefore, whether these findings are applicable to present-day units performing 90% of their prostatectomies by TURP.

These data do not provide a cogent argument either in favour of performing more open prostatectomies or of performing a randomised trial between open prostatectomy or TURP, but they do suggest that we need more information about the risk factors associated with these late deaths and about the metabolic effects of prostatectomy.

Urethral strictures

Urethral strictures are more common after TURP than after retropubic prostatectomy, but they are also common after transvesical prostatectomy (Roos and Ramsay, 1987). Many authors have reported rates of 3 to 4% after TURP (Bergman *et al.*, 1955; Roos and Ramsay, 1987) but the true incidence is much greater. It was 16% when men with low measured flow rates after operation underwent urethroscopy (Schultz *et al.*, 1989). It is possible to reduce the incidence of urethral strictures by performing a preliminary distal internal urethrotomy (Emmett *et al.*, 1963; Schultz *et al.*, 1989). In addition, bladder neck stenosis is more common in the man with a small prostate who is more likely to undergo TURP.

Other problems

The occurrence of genuine stress incontinence owing to sphincter weakness should be a rarity after either operation. It is a consequence of technical error, but incontinence may also be related to bladder storage problems such as detrusor instability. Up to 29% of men undergoing prostatectomy have some degree of urge incontinence before operation and this may persist in 10% (Neal *et al.*, 1989). In one recent study, 4% of men who were dry before operation experienced some degree of incontinence afterwards (Fowler *et al.*, 1988), but this can also be a feature of men with detrusor instability.

Erectile and ejaculatory problems (5 and 60% respectively) after prostatectomy have received increasing attention over the past few years, but appear to have a similar incidence after either procedure.

Clinical Outcome

There is no evidence of major differences in the symptomatic or urodynamic outcome between TURP and open prostatectomy (Meyhoff, 1987), although peak urinary flow rates after open prostatectomy are slightly greater than after TURP (Nielsen *et al.*, 1989), suggesting that an open operation is more frequently complete (see below).

Assessing outcome after operation is not easy when the natural history of the condition is poorly documented and when the end-points are ill-defined. The placebo effect of prostatectomy is likely to be important, but its duration and magnitude are uncertain. The early results of balloon dilatation suggest that improvements in symptoms (rarely their resolution) occur in about 50% of men and peak flow rates increase from about 9 to 12 ml/s, but there is little or no change in voiding pressures. It seems likely, therefore, that the placebo effect of prostatectomy lies between these results and those found in the placebo group of men studied in drug trials. Undoubtedly, pharmacological agents and intra-urethral devices or balloons will be competing with prostatectomy in the future as the stock treatment for outflow obstruction. They do not approach the degree of success achieved by prostatectomy, but it will prove necessary to have a firm grasp on the realities of the outcome of prostatectomy.

In the first place, symptomatic outcome is related to the severity of the original complaint: patient selection matters. One study found that 90% of men with severe symptoms, including retention, had a good outcome (Fowler *et al.*, 1988), whereas only 75% of men with milder symptoms did well. Significant improvement in symptoms is found in 75% of men undergoing elective prostatectomy after 1 year (Neal *et al.*, 1989) and this seems to continue in the long term (Nielsen *et al.*, 1989). About a quarter of men fail to do well, even taking into account the fact that urethral strictures or bladder neck stenosis impair the outcome until they are dealt with.

Men with a poor outcome can be classified into various groups. Some have symptoms of poor flow and hesitancy which may be caused either by persistent obstruction owing to technical imperfection or by weak detrusor function present before operation. Others have irritative symptoms caused by persistent obstruction owing to technical imperfection, or unobstructed instability present before operation. Persistently high voiding pressures and low flow rates, presumably because of incomplete resection, were found in about 5% of men after TURP, but fewer than half of them had a poor symptomatic outcome (Neal *et al.*, 1989). However, weak detrusor function leading to a poor outcome (reflecting deficient patient selection) was much more common. If men without bladder outflow obstruction, who perhaps have detrusor failure or detrusor instability not associated with obstruction, undergo TURP or open prostatectomy—a procedure intended to improve outflow obstruction—it is unlikely they will experience resolution of their symptoms. Unfortunately, whilst pre-operative factors such as weak detrusor contraction or detrusor instability probably play an important role in the high reoperation rate after TURP, these men cannot yet be readily identified before operation.

There is no doubt that we shall have to try harder in the future to improve patient selection in order to identify men who will have a poor outcome, particularly as these men swell the numbers undergoing repeat operation because of an incomplete resection.

The Size of the Prostate and Repeat Operation

Prostatic size measured by examination under anaesthesia correlates with voiding pressures and flow rates, but the small prostate can also cause severe obstruction. On the other hand, men who after operation fail to do well because of poor flow tend to have a small prostate (Dorflinger *et al.*, 1988) and weak voiding pressures before operation (Neal *et al.*, 1989). Presumably, some have weak detrusor contraction rather than obstruction as the cause of their symptoms.

Only 20% of men with outflow obstruction have prostates greater than 60 g and fewer than 4% have glands greater than 100 g (Turner and Belt, 1957; O'Connor *et al.*, 1963; Berry *et al.*, 1984). Few urologists would argue, therefore, that more than 25% of men with outflow obstruction are even suitable for open prostatectomy because the operation is difficult and more likely to lead to incontinence or bladder neck strictures in men with small glands. However, despite oft-repeated denials, many TURPs must be incomplete, particularly when the less experienced or less skilful surgeon confronts the bigger gland. Thus, in units treating between 80 and 95% of men by TURP the mean resected weight varies from 38 g (Bergman *et al.*, 1955), 20 to 25 g (Melchior *et al.*, 1974; Mebust *et al.*, 1989; Neal *et al.*, 1989) to about 12 g (Chilton *et al.*, 1978). The weight removed by open operation for the bigger glands in units carrying out TURP in 80 to 95% of men varies from 40 g to over 70 g (O'Connor *et al.*, 1963; Chilton *et al.*, 1978).

Reoperation after open prostatectomy and TURP

On the face of it, the most serious criticism of TURP (based on hard evidence) comes from the finding that after 8 years, 1 in 10 to 1 in 5 men after TURP undergoes repeat prostatectomy, a 3 to 5 times excess risk compared with that after open operation (Roos and Ramsay, 1987; Wennberg *et al.*, 1988; Nielsen *et al.*, 1989; Roos *et al.*, 1989). Each subsequent procedure is likely to increase the death rate, particularly as the patients will be older, and after TURP more men undergo repeat cystourethroscopy—not only because of urethral strictures. Unfortunately, the situation is more complex than an initial inspection of the figures might suggest.

In the first place, we do not yet know whether these men get better after their second operation. Indeed, we do not know the extent of the repeat operation. One suspects that in some cases a cystoscopy, performed because of persistent symptoms after prostatectomy, is converted into a repeat resection or bladder neck incision more in the vague hope of relieving symptoms than in the well founded expectation of achieving a good outcome. Furthermore, the unhappy patient referred for a further opinion after his third or fourth TURP has failed to relieve his poor stream or urgency, or worse after it has made him wet, might argue that his repeat operation, and possibly his first, was not justified. We need to do better in selecting men before operation for elective prostatectomy. We should investigate carefully the man who has persistent symptoms after operation; by all means perform a cystoscopy to exclude a large residual adenoma, but we should be clear in defining the indications for repeat prostatectomy.

The causes of the repeat operations need to be addressed speedily but carefully. Further research is necessary to determine whether the high rate of revision is inherent in the procedure, whether it is surgeon-related and a result of an imperfectly performed operation, whether it is limited to the larger gland which might be better treated by open operation or whether it is more common in very small glands which might be subject to subsequent bladder neck stenosis and would have been better treated by bladder neck incision. If most repeat operations are the product of an incomplete resection and the subsequent operations are successful, then a reappraisal of the role of TURP in the larger gland would be indicated.

It may be the case that some men destined for an unsatisfactory outcome may be intrinsically more likely to undergo TURP rather than open operation because of other factors present before operation. It has been pointed out above that certain men with low voiding pressures tend to have small prostates—and have a poor outcome. Some of these men are not obstructed and their symptoms of instability may possibly be due to unsuspected and cerebrovascular disease. Does this explain the poor symptomatic results and increased risk of cardiovascular death in some patients after prostatectomy? Because of their small prostates, it is likely that these men undergo TURP rather than open operation. In the past, when the importance of low voiding pressures and unobstructed instability in the causation of symptoms after operation was not widely understood, these men will have been vulnerable to further cystoscopy and repeat prostatectomy. Moreover it is possible that a surgeon is more likely to perform a speculative TURP rather than an open procedure on the doubtful candidate. The fact that some men have a poor outcome after TURP and, therefore, undergo repeat cystoscopy and limited resection does not imply that all, or most, would have been better served by open operation.

Conclusions

Both TURP and open prostatectomy have their respective roles to play in the treatment of men with outflow obstruction. However, much remains unknown about the pathophysiology of outflow obstruction and much is yet to be learnt about the outcome of prostatectomy. The excess risk of death in the first 3 months after prostatectomy, after both types of operation, should stimulate further study. The reasons for the apparently increased late death rate in men undergoing TURP also need to be identified. In particular, we need to know the reasons for the high rate of reoperation after TURP. Most importantly, in order to decrease the number of men with a poor outcome after operation, we need a way of improving selection for prostatectomy.

There is no boulder in our pond, nor is our boat being rocked. These studies into mortality and reoperation, acting in concert with other recent studies of pathophysiology, patient selection and outcome, are merely forcing the pace of the present reappraisal of TURP. The lesson is that only hard data and well designed studies can settle those controversial issues so often hidden in the heart of standard surgical practice: clinical practice needs to walk hand-in-hand with clinical research. The challenge ahead is to ensure that our new training programme, in addition to providing a high quality surgical education and a test of ability to navigate well charted waters, also encourages those of an inquiring disposition.

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The Author

D. E. Neal, MS, FRCS, BSc, Senior Lecturer in Urology and Honorary Consultant Urological Surgeon, University of Newcastle upon Tyne and Freeman Hospital.

Requests for reprints to: D. E. Neal, Department of Urology, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN

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Family Screening for Duplex Kidneys

EILEEN M. O'NEILL

Department of Paediatrics, Barnsley District General Hospital, Barnsley

Summary—Family screening was offered to the relatives of 57 patients with duplex renal systems and this resulted in the detection of another 37 cases. A further 5 first degree relatives had abnormal intravenous urography, so that 25% of the screened relatives had significant renal abnormalities. It is suggested that there may be a place for screening the whole family if renal tract duplex is detected.

Paediatricians aim to send children into adulthood as healthy as possible and it is challenging to deal with occult abnormal conditions that can have a devastating effect in adult life.

The renal tract is no longer hidden antenatally now that scanning is readily available, but only relatively gross abnormalities are usually detected by this method. More often, children are born with renal tract anomalies and no clinical evidence that anything is wrong. The delay in diagnosis can result in significantly scarred kidneys that can affect the patient seriously in later childhood or adult life.

There may be clues to a possible renal problem in childhood but these are often ignored at the time. There are few clues to renal problems before the first clinical evidence appears but one exception is a family history of renal anomalies. This survey dealt with family screening and duplex renal systems.

Patients and Methods

The survey took place between September 1967 and July 1979. Index cases were consecutive patients found to have unilateral or bilateral duplex renal systems on routine clinical assessment for symptoms or signs referable to the renal tract. Those with only pelvic duplex were excluded if the diagnosis was doubtful.

Duplex systems were explained to the parents of index cases, with diagrams, and they were told of the possibility that other family members could be affected unbeknown to them but that duplex renal systems are not necessarily associated with renal problems. They were then offered screening by limited intravenous urography (IVU) of other family members, including siblings yet to be born. Newborn siblings were assessed and if clinically normal, with normal urine and urea, IVU was delayed for a few weeks to fit in with the requirements of their parents. If there was abnormality of any newborn with possible renal tract involvement, IVU was not delayed unless clinically indicated. Affected index patients and siblings were managed in the renal clinic. Affected adult family members had blood pressure, midstream urine and urea assessments if they were available and their family doctors were informed of the findings.

A total of 57 index cases and 168 relatives were assessed.

Results

Table 1 shows the number of cases with duplex renal systems together with 5 other renal abnormalities (see below). There were 57 index cases, but the addition of family screening resulted in the detection of a total of 99 patients with renal anomalies. Screening of the 168 relatives was divided almost equally between the sexes but duplex systems were found in about twice as many females as males.

When the family surveys were complete (Table 2) and taking into consideration only the index cases and first degree relatives, there was a predominance of females in the index cases and parents. As many relatives (32) were found to have duplex systems as index cases (32), although only a

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Table 1 Cases with Unilateral or Bilateral Duplex Renal Systems

	No. screened			*No. affected*		
	Males	*Females*	*Total*	*Males*	*Females*	*Total*
Index cases	—	—	—	15	42*	57
Siblings	44	40	84	6	9*	15
Parents	35	41	76	5	13	18
Grandparents	1	2	3	0	1	1
Cousins	3	1	4	1	1	2
Aunts/uncles	0	1	1	0	1	1
All relatives	83	85	168	12	25	37
Other renal radiological abnormalities	—	—	—	2	3	5
Total	—	—	—	29	70	99

*Includes one pair of identical twins.

Table 2 Family Surveys Complete (i.e. both parents and all siblings)

	No. with duplex systems		
	Males	*Females*	*Total*
Index cases	8	24	32
Siblings	6	7	13
Parents	4	11	15
Grandparents	0	1	1
Cousins	1	1	2
Aunts/uncles	0	1	1
Total	19	45	64

few of the second degree relatives were assessed. In addition, there were 4 index cases with unilateral duplex in whom the single duplex system in a parent affected the opposite side.

Of the 36 index cases who underwent cystourethrography (MCU), 21 had reflux and 18 reflux into duplex systems (Table 3).

Urine infections were diagnosed if a midstream or clean catch urine contained a pure growth $>10^5$ organisms/ml. Table 3 shows that 41 of the 57 index cases had proven urine infections and 7 had more than 3 such infections; these were found on monthly testing until 12 months clear of infection had elapsed, with extra tests between appointments if urinary symptoms developed.

The non-duplex unsuspected IVU anomalies in relatives of index cases were hydronephrosis due to a pelvic mass in a mother, a staghorn calculus and hydronephrosis in 2 brothers and a scarred kidney and reflux with hydronephrosis in 2 sisters.

Discussion

This survey has demonstrated that it is worthwhile to screen family members of patients known to have duplex renal systems. A further 37 cases of renal duplex were detected, 33 of which were in first degree relatives of the 57 index cases. No attempt was made to assess all 37 cases for complications which were unlikely to be different from those of the index cases.

Duplex systems are prone to infections and these may be associated with vesicoureteric reflux and obstruction (Atwell *et al.*, 1974; Stephens, 1986) or other renal tract anomalies (Stephens, 1986). If untreated, chronic pyelonephritis may ensue with possible hypertension and renal failure. This series

Table 3 Index cases with (a) Ureteric Reflux and (b) Proven Urine Infections

	Males	*Females*
(a) Ureteric reflux		
Into duplex system(s)	4	14 (5)
Into opposite single system only	1	2
No reflux	2	13
No MCU done	8	13
Totals	15	42
(b) Proven urine infections		
Nil	6	10
1–3	8	26
>3	1	6
Total	15	42

Number in brackets indicates reflux also into an opposite single renal system.

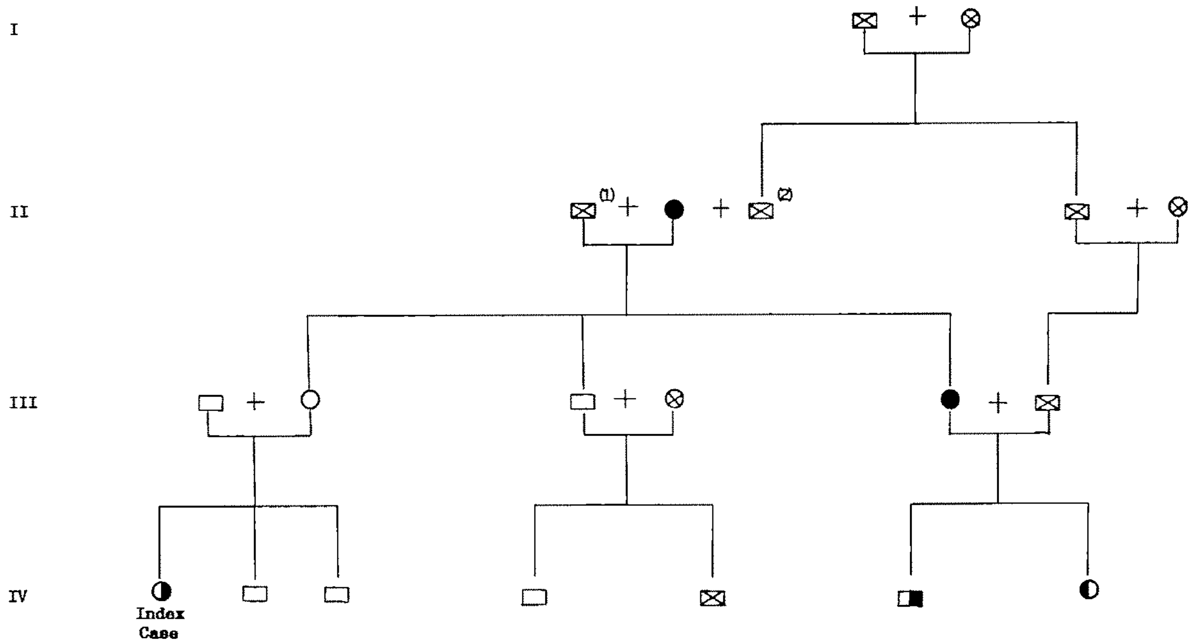

Fig. Degrees of penetrance of dominant gene

⊠ = Male and ⊗ = Female—Not screened
□ = Male and ○ = Female—Screened and not affected.
■ and ● = Bilateral duplex.
◧ and ◐ = R. duplex.
◨ and ◑ = L. duplex.

supports that of Atwell *et al.*, (1974) in which they found previously undiagnosed pyelonephritis and reflux in screened first degree relatives of their 30 index cases.

Whitaker and Danks (1966) reported the inheritance of duplication of the kidneys and ureters. There were 39 consecutive index cases. Duplex renal systems, excluding isolated duplex renal pelves, were found in 16/123 IVUs (13%) done on relatives. In the present series, 37 relatives with duplex renal systems were found in the 168 IVUs (22%). Adding 5 other renal abnormalities in relatives of index cases, 25% (42/168) were abnormal. Excluding the 14 relatives with definite duplex pelves only, there remained 28 abnormal IVUs (16.7%), 23 of these (13.7%) being due to duplex kidneys and ureters, a percentage similar to that of Whitaker and Danks (1966). Stephens (1986) defined with diagrams duplex renal systems, including pelvic duplex only as the least severe form. In the study now reported there was no doubt that isolated pelvic duplex was part of the pattern of inheritance, it being present in 14 of 37 relatives with duplex systems. In addition, 1 index case had a left duplex kidney and ureter and her identical twin had a right duplex pelvis only. Atwell *et al.* (1974) found a duplex system in 11/101 index patient's relatives, excluding bifid renal pelves, but 32/101 if isolated bifid pelves were included. It is therefore felt that pelvic duplex should always be included in genetic and clinical assessments of renal duplex systems.

Autosomal dominant gene inheritance of duplex kidneys and ureters with variable degrees of penetrance was suggested by Whitaker and Danks (1966) and they calculated a 1 in 8 chance of duplication in siblings or parents but excluded isolated pelvic duplex. Atwell *et al.* (1974), in their study of 30 index cases, found support for the hypothesis of dominant inheritance with variable penetrance and suggested routine screening of siblings for duplex urinary tracts. In studying the epidemiological and genetic aspects of congenital urinary tract malformations and their familial incidence, Bois *et al.* (1975) found a 5.3% ureteric and pelvic duplication rate in first degree relatives of 25 index cases, but it is not clear if all degrees of duplex were included. Atwell *et al.* (1977), in a further study, again found evidence for inheritance by autosomal dominant genes of variable penetrance but for both duplex systems and primary ureteric reflux on this occasion.

Variable degrees of penetrance of the dominant gene are demonstrated in the Figure, in which there were 4 subjects with recognised duplex systems in the extended family of the index case whose parents and brothers were not affected.

In the present series, 4 index cases with unilateral duplex had a parent who had unilateral duplex but affecting the opposite side. This lack of lateralisation in some families with renal system duplex, which is also demonstrated in the Figure, could be explained by the dominant gene inheritance being a potential bilateral defect but with incomplete penetrance affecting either side in some, so producing only unilateral duplex as seen in many patients.

The evidence suggests there may be a place for screening the whole family if renal tract duplex is confirmed. The least invasive but most reliable available method should be used.

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The Author

Eileen M. O'Neill, MD, FRCP, DCH, Consultant Paediatrician Emeritus.

Requests for reprints to: Eileen M. O'Neill, 5 Amberley Gardens, Bedford MK40 3BT.

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Dilatation in the Duplex Kidney: 3 Unusual Cases

JANET E. PAGE and C. JEAN DOW

Department of Diagnostic Radiology, St George's Hospital, London

Dilatation in the upper limb of a duplex ureter is usually secondary to obstruction and may be associated with a ureterocele. By contrast, vesicoureteric reflux is the usual cause of a dilated lower moiety ureter. We report 3 cases in which unusual or complex causes of dilatation of 1 limb of a duplex ureter were demonstrated.

Renal duplication is the commonest congenital abnormality of the renal tract (Hartman and Hodson, 1969; Bissett and Strife, 1987). In complete duplication the ureters insert separately into the bladder with the ureter draining the upper moiety located below that of the lower moiety; the latter is usually normally located at the trigone (Persky and Noseworthy, 1976; Young and Lebowitz, 1986). Urinary tract anomalies are present in approximately 17% of children with complete duplication (Bissett and Strife, 1987). The ectopic ureter may be associated with a ureterocele and dilatation of the upper segment usually relates to obstruction (Young and Lebowitz, 1986; Sutton, 1987). Dilatation of the lower moiety commonly results from reflux secondary to a shorter insertion of the normally placed ureter. (Bissett and Strife, 1987; Sutton, 1987).

We present 3 patients in whom unusual causes of dilatation of 1 limb of a duplex system were demonstrated. Two cases involved the upper moiety. One was caused by reflux from an ectopic ureter inserted into the urethra and the other was secondary to obstruction from a carcinoma arising at the junction of an incompletely duplicated ureter. The third patient developed a pelviureteric obstruction in the lower moiety and this was associated with reflux nephropathy.

Case Reports

Case 1. A 26-year-old woman gave a history of recent urinary infections; there was no history of childhood infections and the patient was continent. An intravenous urogram showed a normal right renal tract. The left system was duplex with a poorly functioning dilated upper moiety (Fig. 1). The ureter draining this segment was not visualised but was demonstrated at a subsequent micturating cystourethrogram and was inserted ectopically into the urethra above the sphincter. It was very dilated and was shown by reflux during micturition only (Fig. 2). There was no associated ureterocele and the patient was continent.

Case 2. A 65-year-old man complained of 2 days' painless

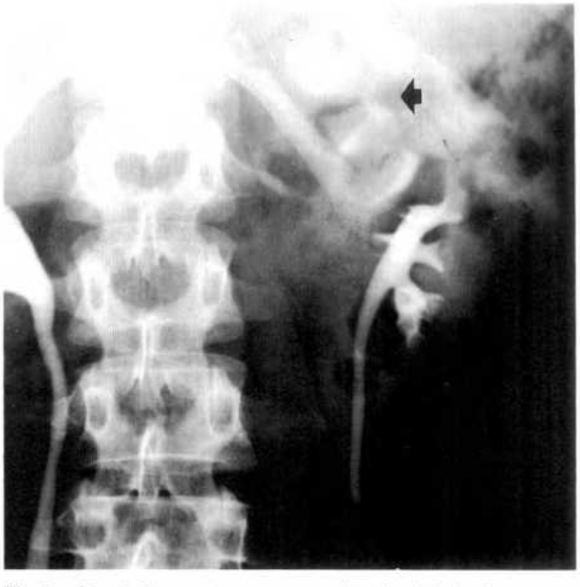

Fig. 1 Case 1. Intravenous urogram showing left duplex system with poorly functioning dilated upper moiety (arrow).

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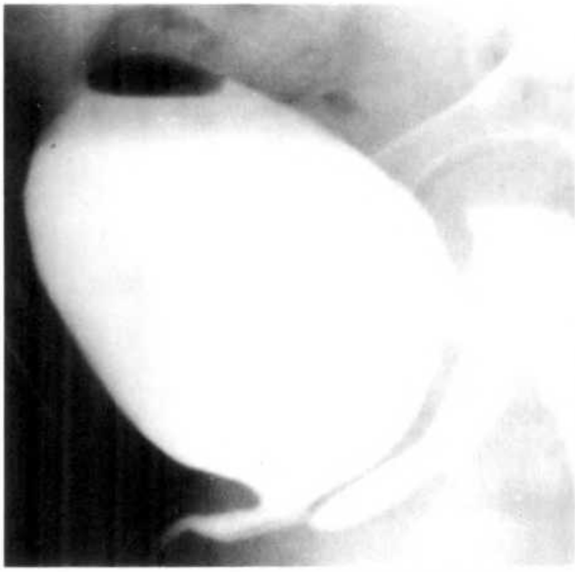

Fig. 2 Case 1. Ectopic insertion of dilated upper moiety ureter into the proximal urethra demonstrated during micturition.

haematuria. He was on long-term oral anticoagulants following a previous history of pulmonary emboli. His therapy was well controlled and clinical examination was normal.

Intravenous urography showed that the right renal tract was normal. There was a partial duplex system on the left with the ureters joining at the level of L5. The upper moiety pelvis and ureter were dilated and an obstructing intraluminal filling defect was demonstrated at the junction of the 2 ureters (Fig. 3). The lower moiety pelvis and draining ureter and the single ureter distal to the lesion were all normal.

At surgery a tumour was seen to arise from a narrow pedicle at the junction of the 2 ureters and was obstructing the upper pole only. It was excised and a side-to-side anastomosis was performed between the 2 ureters. Histology was that of a moderately differentiated papillary transitional cell carcinoma.

Case 3. A 24-year-old woman gave a history of longstanding recurrent urinary tract infections. Urography showed a normal left system and a duplex right side. The upper segment was normal but the lower segment was dilated with the appearance of a pelviureteric junction obstruction; the draining ureter was not demonstrated (Fig. 4). A DTPA renogram showed a deficient nephrogram in this right lower pole, poor clearance from the pelvicaliceal system, a rising curve and no response to frusemide. Retrograde examination showed that the ureters joined just proximal to their entry into the bladder. A micturating cystourethrogram failed to demonstrate reflux but a DMSA study showed scarring of the cortex of the lower moiety. This segment and its ureter were excised and histology showed changes consistent with reflux nephropathy.

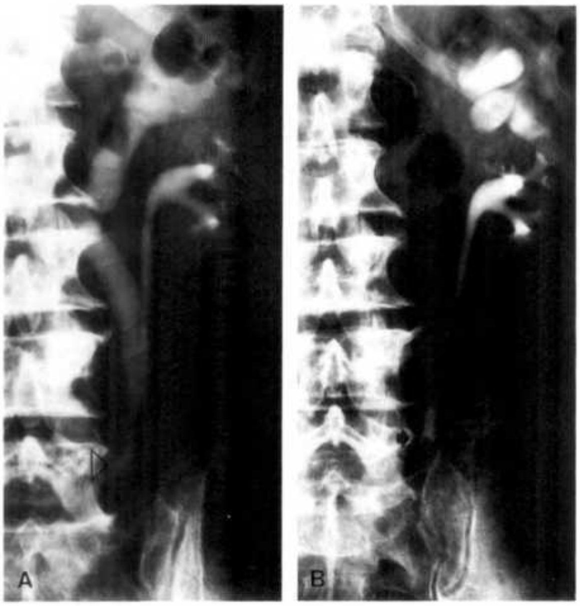

Fig. 3 (A) Case 2. Partial duplex left system with dilated upper moiety ureter down to its junction with the lower moiety at L5 (arrow). (B) The intraluminal filling defect is shown at this level on the 20-min film (arrow).

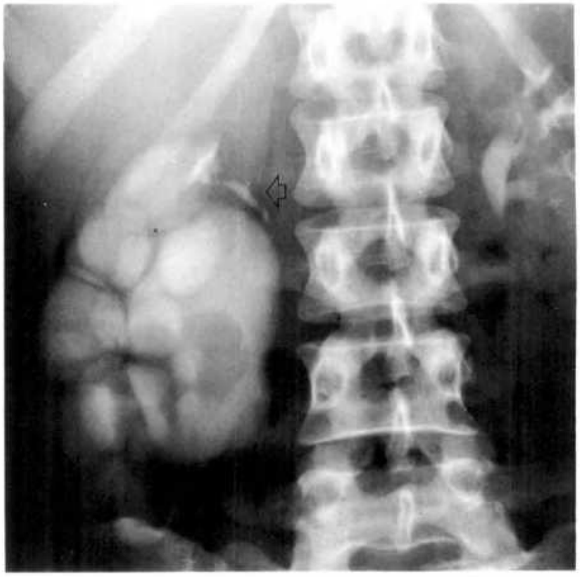

Fig. 4 Case 3. Apparent pelviureteric junction obstruction involving the lower moiety ureter of a duplex right system. The upper moiety is seen as an irregular crescent of contrast (arrow).

Discussion

Dilatation of 1 moiety of a duplex system may be secondary to either obstruction or reflux. The ureter draining the lower moiety, although normally located, has a shorter intramural course at the vesicoureteric junction and is more prone to reflux and infection (Bissett and Strife, 1987, Sutton, 1987). When complete duplication is present it is the ureter draining the upper moiety that is ectopic (Persky and Noseworthy, 1976; Young and Lebowitz, 1987); the pelvicaliceal system associated with it is frequently abnormal (Yue, 1974). Ureteroceles may be present and are often associated with a dysplastic or obstructed upper moiety, or both (Young and Lebowitz, 1986; Sutton, 1987). In young children they can be associated with bladder outflow obstruction (Williams and Woodard, 1964; Sutton, 1987). To complicate the issue further, ectopic ureteroceles, unlike simple ureteroceles, frequently reflux. Ectopic ureters are more common in females (Sutton, 1987).

Ectopic ureters are often associated with recurrent urinary tract infections and ureters inserted into the bladder neck or urethra can reflux on voiding (Sutton, 1987), as illustrated in Case 1. This may be difficult to demonstrate, although it is suggested that it may occur in approximately one-third of cases (Wyly and Lebowitz, 1984). The ectopic ureter may insert anywhere along the genitourinary tract (Sutton, 1987), classically giving rise to symptoms of wetness or dribbling since childhood (Persky and Noseworthy, 1976; Young and Lebowitz, 1986). Incontinence is not always present, however, and patients may present with other genitourinary symptoms, for example vaginal discharge (Persky and Noseworthy, 1976). In one series, urinary incontinence was regarded as significant only when the ectopic ureter was inserted into the distal urethra (Persky and Noseworthy, 1976). Vesicoureteric reflux and obstruction at the pelviureteric or vesicoureteric junctions may coexist (Leighton and Mayne, 1989). Case 2 illustrates a pelviureteric junction obstruction in a lower moiety which showed evidence of reflux nephropathy on histology. All anomalies which affect the unduplicated single ureter may affect the lower moiety of a duplex system, including pelviureteric junction obstruction (Young and Lebowitz, 1986). Reflux is a common finding in duplex kidneys, with an increased incidence in complete duplication. The lower moiety ureter is usually affected (Bissett and Strife, 1987). Pelviureteric junction obstruction is rare and again more commonly affects the lower moiety ureter (Mesrobian, 1986). The 2 events may coexist coincidentally or they may be causally related (Rickard and Whitaker, 1984). Severe vesicoureteric reflux may distend the pelviureteric junction and result in obstruction (Rickard and Whitaker, 1984). The mechanism is unclear, but is thought to be related to atonicity and angulation at the pelviureteric junction, together with an active process (Whitaker, 1970).

Transitional cell carcinoma of the ureter accounts for less than 1% of malignant tumours of the urinary tract (Tudor and Clear, 1986). It is rare in 1 limb of a duplex ureter. In 2 previously reported cases (Tudor and Clear, 1986; Sreenevasan *et al.*, 1987), presenting complaint was painless haematuria and tumour was found in the distal part of the lower moiety ureter, 1 of which was causing obstruction. Tumour occurring at the junction of incompletely duplicated ureters has not been described before, although congenital strictures can be seen here (Hartman and Hodson, 1969). There is no direct evidence of an increased incidence of carcinoma in a duplex system, although it is suggested that the prevalence of urinary tract infection associated with structural renal tract abnormalities may predispose to complications such as stone formation and transitional cell carcinoma. In the case of the partially duplicated ureter, reflux between the 2 limbs (the "yo-yo" effect) may be implicated in the development of such complications, particularly if the urine is infected (Hartman and Hodson, 1969).

In conclusion, determination of the exact aetiology of a dilated moiety in a duplex system has an important role to play in the management of these patients. Obstruction and reflux may co-exist and the relative contribution of each affects treatment (Whitaker and Flower, 1979; Leighton and Mayne, 1989). The 3 cases described above illustrate unusual manifestations of the complications which can be seen in the duplex renal system.

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The Authors

Janet E. Page, MRCP, FRCR, Senior Registrar.
C. Jean Dow, FRCP, FRCR, Consultant Radiologist.

Requests for reprints to. Janet E Page, Department of Diagnostic Radiology, St. James' Wing, St George's Hospital, Blackshaw Road, London SW17 0QT.

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Crystalluria, Medullary Matrix Crystal Deposits and Bladder Calculi Associated with an Acutely Induced Renal Papillary Necrosis

P. H. BACH

Nephrotoxicity Research Group, Robens Institute of Health and Safety, University of Surrey, Guildford

Summary—A single (100 mg/kg) intraperitoneal dose of 2-bromoethanamine hydrobromide induced renal papillary necrosis (RPN) acutely in rodents and caused a transient crystalluria between 4 and 8 h after dosing. These crystals comprised struvite or magnesium ammonium phosphate (MAP) as assessed by shape, solubility, infra-red spectrum and X-ray microprobe analysis. Acid-soluble, bi-refringent crystals were also present within the renal medullary matrix during the same time period as the crystalluria. The presence of the MAP was associated with loss of the anionic renal medullary mucopolysaccharides staining. A total of 5/64 rats with a 2-bromoethanamine-induced renal papillary necrosis and monitored for up to 160 days had bladder calculi that were predominantly MAP. These data suggest that medullary mucopolysaccharide matrix disruption associated with RPN leads to a release of previously bound cations, supersaturation and the nucleation of crystalline MAP. These processes could also be implicated in the formation of MAP bladder calculi.

There has been little investigation into the most important factors underlying the relatively high incidence of renal calculi and bladder stones (Hare and Poynter, 1974) reported in chronic analgesic abusers (Bach and Bridges, 1985). It is, however, commonly assumed that calcification of damaged tissue, such as papillary ghosts (Burry *et al.*, 1977), altered renal electrolyte handling, particularly calcium wastage (Jaeger *et al.*, 1982) and recurrent urinary tract infection (Dubach *et al.*, 1983; Eknoyan, 1984), contribute to the multifactorial processes that cause a high incidence of urolithiasis in this group of patients.

Attempts to induce papillary necrosis experimentally by the administration of mixed analgesics to rodents have met with only moderate success (Rosner, 1976; Bach and Hardy, 1985). Despite this general failure to reproduce renal papillary necrosis in laboratory animals using analgesics *per se* (Bach and Hardy, 1985), there are a number of strategies that can be used to produce models of analgesic nephropathy (Bach and Gregg, 1988). These include a single parenteral administration of ethyleneimine (Bach and Bridges, 1985) or 2-bromoethanamine hydrobromide (Bach *et al.*, 1983), which will cause a dose-related total necrosis of the papilla in 24 to 48 h. Daily administration of N-phenylanthranilic acid, a fenamic acid analogue, given by gavage (Hardy & Bach, 1984), causes a dose-related, apex-limited necrosis, but requires up to 14 days' treatment. Of these the 2-bromoethanamine (BEA) model has been most widely investigated (Bach and Bridges, 1985). Routine studies on the pathogenesis of 2-bromoethanamine-induced RPN in this laboratory have shown a marked crystalluria shortly after dosing. Calculi have occasionally been found in animals over several months after an acutely induced RPN, but never in control animals followed for up to 6 months. The purpose of this investigation was to define the chemical composition of urinary crystals, to study the time-course of their formation following administration of BEA, and to identify the inorganic components of the associated bladder calculi. Urinary crystals were identified by their shape, solubility, infra-red spectrum and X-ray micro-

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probe analysis; in bladder calculi the inorganic constituents were identified by their infra-red spectrum and by X-ray microprobe analysis. In both cases struvite, or magnesium ammonium phosphate, was shown to be the most prominent inorganic component, the release of which was associated with changes in the medullary glycosaminoglycan matrix. A better understanding of the processes leading to the formation and deposition of this material offers the potential to develop a useful animal model to study the factors affecting urolithiasis in analgesic abusers.

Materials and Methods

Magnesium ammonium phosphate, calcium oxalate, uric acid, xanthine, acetone, chloroform, diethyl ether, ethyl alcohol, acetic acid, 0.1 N-NaOH and 0.1 N-HCl were of analytical purity and potassium bromide was infra-red grade (BDH, Poole). 2-Bromoethanamine hydrobromide was purchased from Aldrich chemicals (Poole).

Experimental animals

Groups of treated and control (n = 4) University of Surrey strain, male Wistar rats were randomly assigned and allowed 4 to 7 days to acclimatise. Animals were housed in translucent "shoe box" type cages, using ethylene oxide-sterilized soft wood shaving (Lee and Son, Chertsey) bedding, which was changed weekly. Animals were kept in a strict 12-h light/dark cycle (light cycle starting at 0700 h GMT) and given tap water *ad libitum* throughout these investigations; they were maintained on Lab Diet 1 (Spratts, Barking) rat cubes (while in cages) or Lab Diet 2 (Spratts, Barking) powdered diet (in the metabolic cages). In one experiment, diet was withheld for 24 h before and 8 h after dosing to reduce solid particulate contamination of the urine. The rats were handled regularly during the course of the acclimatisation period to minimise stress responses during investigations (Gartner *et al.*, 1980). Urine collection was undertaken in a Techniplast metabolic cage (code 1700872 Forth-Tech Services, Dalkeith) designed to separate urine and solid material. Spontaneously voided urine was collected at 4, 8, 12, 24, 48 and 72 h, volumes measured and spot pH measurements made using a conventional single microelectrode. Osmolality was measured by freezing point depression using an Advanced Instruments Digimatic Osmometer (Needham Heights, USA), using a series of standards of 200, 600 and 1200 mOsmol/kg. Urine was immediately centrifuged at 3000 × g for 10 min and the particulate material washed twice by resuspension in distilled water. Any solids were resuspended in 0.5 ml distilled water and examined under a phase contrast microscope (Leitz, Luton) in a single drop of liquid that could be removed by filter paper and flooded with solvents or dilute acid/base to assess the solubility characteristics.

Animal dosing

Rats (200–220 g) were dosed intraperitoneally, between 0900 and 1100 h, with a single injection of 100 mg/kg BEA freshly dissolved in 0.9% (m/v) NaCl and used within 5 to 10 min.

Long-term studies

Groups of animals that had been dosed with a single intraperitoneal injection of 100 mg/kg BEA for other experiments that required terminal kills between 20 and 160 days were carefully assessed for the presence of bladder or renal pelvic calculi. The number of animals in each of 3 time spans were 20–40 days (n = 32), 41–80 days (n = 19) and 81–160 days (n = 13), with 14, 7 and 4 controls respectively. The bladders of animals used for these long-term investigations between 20 and 160 days after treatment were examined for solid material. Calculi were washed in distilled water, dried and kept for infra-red and X-ray microprobe analysis.

Autopsy and histology techniques

Groups of 3 rats were killed at 6, 12, 24 and 72 h after BEA dosing. Kidneys were fixed in phosphate buffered neutral 10% (v/v) formaldehyde for 18 to 24 h, dehydrated and embedded in Fibrowax (Lamb, London) in a Histokinette (British American Optical, Slough). Serial sections of 7 µm thickness were cut on a Spencer 880 microtome (British American Optical, Slough) and stained with haematoxylin and eosin (H and E) according to Pearse (1972). All sections were mounted under coverslips with DPX (Lamb, London). Medullary mucopolysaccharide (the major histochemical constituent of which is glycosaminoglycan) staining was assessed by Toluidine blue metachromasis (Pearse, 1972). The presence of bi-refringent material was assessed in Neutral Red stained sections (that had no other histochemical treatment) using polaroid filters.

Crystal and calculi analysis

The shape and solubility of urinary crystalline sediments were used as a simple means of assessing the major chemical composition for the most commonly encountered urinary sediments (Diem and Lentner, 1970). Infra-red analysis for the identification of the chemical composition of urinary tract deposits was undertaken by the established methods based on the flow chart of Oliver and Sweet (1976) and the published spectra of Weismann *et al.* (1959), Oliver and Sweet (1976), Gault *et al.* (1980) and Modlin and Davies (1981). Crystalline deposits or fragments from calculi (1–2 mg) were finely ground in a micro-agar ball mill with about 200 mg of oven dried infra-red quality KBr for 15 min. KBr discs were made in a vacuum press (Beckman-RIIC, Glenrothes) using a pressure of 7–10 tons/ins^2 for 20 min. Reference spectra were prepared similarly. The discs were scanned on a Perkin Elmer Model-577 Infra-red Grating Spectrophotometer (Perkin Elmer, Beaconsfield). Where necessary an AT-02 attenuator (Beckman-RIIC, Glenrothes) was placed in the reference path to optimise the trace. The sample scanning time was 15 min, with the slit set to normal and the time constant on auto. The calibration of the instrument wavelength was checked with a polystyrene film (Beckman-RIIC) at 1583 and 1601/cm.

X-ray micro-analysis

Micro-X-ray analysis was undertaken by the Micro-structural Studies Unit at the University of Surrey. The calculi or crystal deposits were stuck to a perspex base with double-sided adhesive tape (Scotch pressure sensitive tape, 3M Company), vacuum carbon coated and assessed in a JOEL JXA-50A scanning electron microscope. Spot X-ray analysis was undertaken using a Link 860 System (Link, High Wycombe). The emitted X-rays were monitored for 100s. Heterogeneity was assessed by analysing up to 20 different crystals or 5 different areas on 6–10 fragments from each of the 5 different calculi, and comparing each analysis to the first. The final accumulated analyses (from homogeneous deposits) were plotted from the multichannel analyser of the Link system.

Results

Urinary volume and pH changes

The Table shows the mean changes in the urinary volume, osmolality and pH following BEA dosing. BEA caused a substantial increase in urinary volume, (even within the first 2 h after dosing), reduced the pH and also decreased osmolality to be approximately iso-osmolar with plasma.

Urinary crystals

There was a marked increase in the presence of urinary crystals between 4 and 8 h in all animals dosed with BEA and material was essentially absent after 8 h. The same pattern of crystalluria was noted in experiments where food was withheld over 24 h

Table Effect of BEA on Urinary Volume, pH and Osmolality

	Time period (h)							
	−24–0	*0–2*	*2–4*	*4–6*	*6–8*	*8–24*	*24–48*	*49–72*
Volume (ml)*								
Control	12.3	1.2†	NU	1.6†	NU	12.8	13.4	11.8‡
	±1.3	—		—		±2.9	±1.5	±1.1
Treated	11.8	5.8	6.2	4.5	2.1	16.8§	36.9§	41.3§
	±1.1	±1.4	±2.1	±2.1	±1.8	±3.1	±9.3	±8.4
Osmolality (mOsm/kg)								
Control	891	983†	NU	893†	NU	742	997	930
	±121	—		—		±109	±137	±101
Treated	890	399	289	257	409	297§	285§	364§
	±94	±192	±98	±104	±89	±75	±102	±72
pH								
Control	6.9	6.7†	NU	6.6†	NU	6.6	6.8	6.9
	±0.2	—		—		±0.2	±0.2	±0.1
Treated	6.7	6.4	6.2	5.8	6.4	6.5	6.4	6.7
	±0.1	±0.1	±0.3	±0.4	±0.2	±0.4	±0.3	±0.4

*n = 4 unless otherwise stated, † = Mean of 2 values, ‡ = Data presented as mean ± SD
NU = No urine was voided spontaneously over this period.
§ = Data significantly different from control, $P < 0.05$.

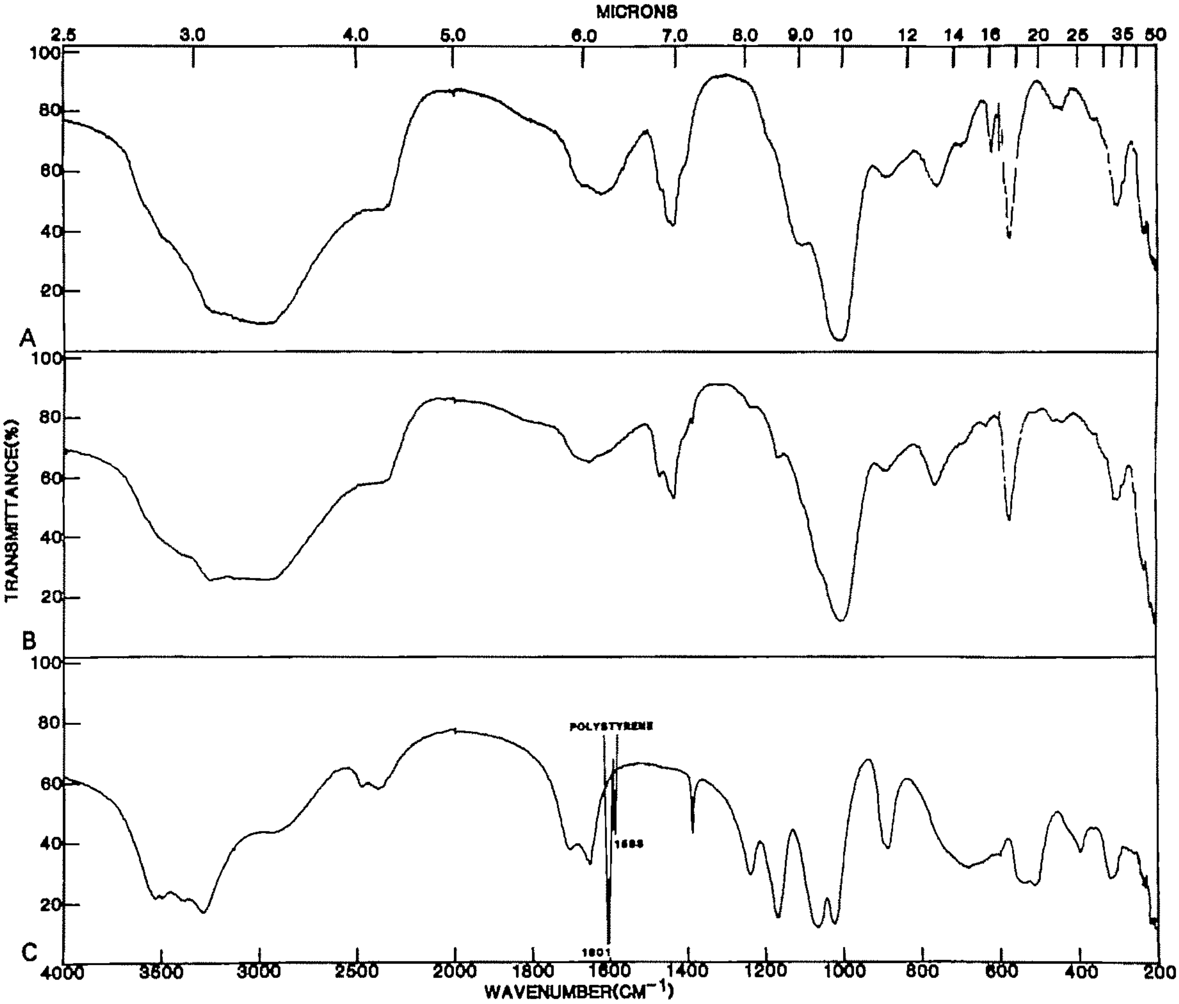

Fig. 1 Infra-red spectrum of (A) urinary crystals harvested shortly after giving BEA, (B) ammonium magnesium orthophosphate (magnesium ammonium phosphate) and (C) typical bladder calculi found up to 160 days after BEA treatment.

before and 8 h after BEA dosing. If urine was left for >8 h there were fewer crystals, probably due to the decrease in urinary pH (by a maximum of 1 unit) following BEA administration and the acid solubility of the crystals.

The shape of the urinary crystalline material was that of classical "coffin lids", which together with the solubility of the material in dilute mineral and acetic acid, but not alkalis, or organic solvents, or on heating in aqueous solution, suggested struvite or magnesium ammonium phosphate hexahydrate (MAP). This was confirmed by infra-red analysis (Fig. 1A), the trace of which differed only slightly from a chemically pure standard (Fig. 1B). The most widely used urological nomenclature will be applied to material of urinary origin, *i.e.* magnesium ammonium phosphate, where the chemical standard is correctly called ammonium magnesium orthophosphate. X-ray micro-probe analysis did, however, show striking differences between the urinary MAP (Fig. 2A), which contained substantial amounts of potassium, and the chemical standard (Fig. 2B), which was potassium-free but contained a trace of chlorine ions.

Bladder calculi

Bladder calculi were found in only 5 of the 64 BEA-treated animals and not in controls. The incidence was as follows: 1/32 (in animals investigated 20–40 days after BEA); 2/19 (41–80 days) and 2/13 (81–160 days); the calculi varied from 1 to 3 mm in diameter. The bladder calculi produced an infra-

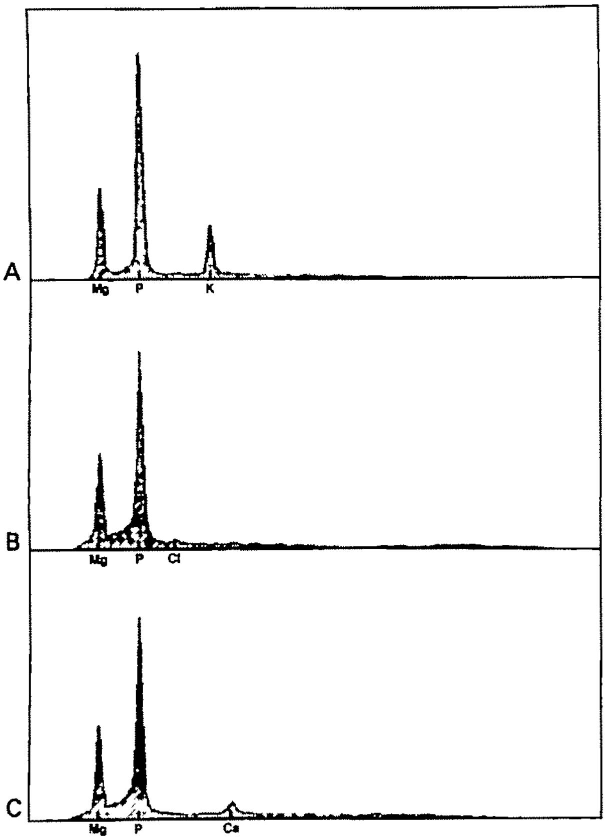

Fig. 2 X-ray micro-probe analysis of ion contents of (A) urinary crystals harvested shortly after giving BEA, (B) ammonium magnesium orthophosphate (magnesium ammonium phosphate) and (C) typical bladder calculi found up to 160 days after BEA treatment

red trace (Fig. 1C) that differed substantially from that of the chemical standard due to the presence of matrix and other inorganic material. The trace showed prominent phosphate absorption at 950 to 1200/cm and a broad area at 2900 to 3250/cm which indicates MAP. The sharp absorption at 1390/cm and the shoulder at 3000/cm suggest that traces of oxalate were present. The X-ray micro-probe analysis (Fig. 2C) confirms the presence of magnesium and phosphate, but also shows a small amount of calcium.

Short-term pathological and histochemical changes

The histological changes associated with the development of the BEA-induced lesion were essentially similar to those described (Bach *et al.*, 1983) and included the earliest loss in the staining of the medullary glycosaminoglycan matrix at 6–12 h, in parallel with the development of the renal papillary necrosis at the apex of the medulla. Necrosis affected the papilla tip at 24 h, and by 72 h this region showed signs of re-epithelialisation. The 6 and 12 h Neutral Red stained sections showed the presence of bi-refringent material in the medullary matrix, but not in cells. This was not strictly related to the regions in which necrosis had taken, or was taking place. Similar crystals were not seen in sections exposed to dilute mineral acid, but they were present after alkali and organic solvent treatment, strongly suggesting that they were MAP. The use of acidic solutions for both H and E and for Toluidine blue metachromasis would have dissolved any crystals from these sections.

Long-term pathological changes

The long-term changes in the kidney are beyond the scope of this study, but included renal scarring, fibrosis and glomerular sclerosis, the frequency and severity of which were time-related. There were also significant numbers of tubular casts. The medullary matrix did not stain for mucopolysaccharides and no acid soluble bi-refringent crystals were present in Neutral Red sections. There was, however, mineralisation of some regions of the medulla. Where the bladder calculi were present they had contributed to mild hyperplasia of the urothelium.

Discussion

Several complementary analytical methods have been used to show that the crystalluria 4 to 8 h after BEA administration represented predominantly MAP. Microprobe analysis showed a substantial amount of potassium (possibly representing a release from injured cells) and traces of oxalate and calcium. The consistent ratio of potassium-magnesium-phosphate measured by X-ray microprobe analysis in all crystals suggests either a mixture of MAP and magnesium potassium phosphate or a magnesium ammonium potassium phosphate complex, neither of which has been described before.

The aetiology of urinary MAP deposits in man is explained by concomitant predisposing factors, most importantly a urinary tract infection with an organism producing urease, that splits urea to ammonium ions. This provides the cation for the complex and increases urinary pH to >7, a factor which encourages the crystals to form because of their acid solubility (Nordin *et al.*, 1979). This scenario cannot explain the acutely induced and short-lived crystalluria following BEA. There was no evidence for any bacterial involvement in the formation of these crystals. The formation of crystals was so rapid after BEA dosing (and so short-lived) that the effect can be assumed to be treatment-related. Furthermore, if urease bacteria had been present, urinary pH would have increased (and not decreased) on standing.

The nucleation of MAP in urine with a reduced pH is difficult to explain, although recent data (Boistelle *et al.*, 1985) have shown that it is possible to form MAP crystals in acidic sterile urine *in vitro* in those instances where super-saturation conditions exist. The relatively rapid dissolution of urinary crystals in the investigation reported here suggests that rapid but relatively short-lived super-saturation conditions may be a key factor, and it is therefore important to ascertain what could contribute to this greatly increased free solute. Recent data from this laboratory (Delacruz *et al.*, 1990, unpublished observations) have confirmed that there is an increase in urinary magnesium following BEA; this support super-saturation as a key factor but does not explain the mechanism.

The BEA-induced loss in medullary glycosaminoglycan staining is a change that biochemically represents desulphation of the matrix (Bach *et al.*, 1989, unpublished observation), as a result of which changes in the polyanionic interstitium would release large amounts of previously bound solutes, so exceeding their solubility product and leading to crystal formation. The acidity of the urine would dissolve these crystals and produce a solute loaded kidney and induce an osmotic flushing. Although there is a decrease in the urinary osmolality, there is a disproportionate increase in the volume. This concept is supported by the marked swelling of the kidneys and the diuresis, although other mechanisms may be involved. There is also a dramatic cryoprotective effect that follows BEA treatment, shown by the inability to freeze kidneys even if liquid nitrogen is used (Bach, 1986, unpublished observations).

The increase in acid soluble bi-refringent material in the matrix of kidney sections 6 h after BEA treatment, reported in this investigation, supports the concept that the crystals are formed within the medulla at an early phase of the development of the lesion. Gregg *et al.* (1990a,b) confirmed that the earliest changes (at 2–4 h) in the medulla following BEA treatment take place in the medullary matrix, using histochemical staining for glycosaminoglycans.

Urolithiasis formation is a complex process associated with super-saturation, the formation of stable crystals, their growth, aggregation and agglomeration. If microcrystals are formed they may re-dissolve or be excreted as such, or may act as nuclei for the growth of larger crystals and eventually calculi (Nordin *et al.*, 1979). All of these are opposed by a variety of factors that include crystal inhibitors and dissolution processes (Nordin *et al.*, 1979). Each of these processes is affected by a variety of geographical/environmental factors, including water quality and dietary inorganic intake (Clapp, 1981), which play an important loading role in saturation and super-saturation in the formation of crystal nuclei.

Inhibitors of crystallisation are the glycosaminoglycans (especially chondrointin and heparan sulphate) which block growth sites and aggregation of calcium oxalate crystals (Robertson *et al.*, 1978; Roberts and Resnick, 1985). There do not appear to be any data on the role of these polyanions on MAP crystal growth or calculi formation.

Calculi rarely occur spontaneously in laboratory animals and it is generally regarded as difficult to induce them at will because of the many variables involved. We have occasionally encountered calculi in animals treated with BEA, a compound that targets the renal medulla and causes a model nephropathy that is essentially the same as the clinical lesion in analgesic abusers. There are no data on the occurrence of calculi in other published studies on chemically induced RPN, but calcification of the renal medulla is not uncommon in this and other types of renal lesions (Bach and Bridges, 1985). Papillary necrosis can, however, also be induced by maintaining rats on a fat-free diet for up to 43 weeks (Burr and Burr, 1929; Molland, 1978). The morphological changes have been described in detail (Molland, 1978) and include degeneration of the interstitial cells and tubular epithelium, hyperplasia of pelvic epithelium, loss of mucopolysaccharide staining from the interstitial matrix and fatty deposits in the cells of the medulla and cortex. McAmis *et al.* (1929) reported the increased incidence of calculi in the renal pelvis, the ureters and the bladder, but explained this on the basis of a concomitant vitamin A deficiency. Thus there is sufficient indication in these experimental systems to suggest that RPN *per se* may be a predisposing factor in the development of mineral deposits in the urinary tract. The feeding of atherogenic diets has, however, been reported to promote lithogenesis in rats and to increase urinary magnesium (Strohmaier *et al.*, 1985) as over 70% of the renal pelvic mineralisation was MAP (Nelde *et al.*, 1985). Thus there are a number of circumstances in the rat where MAP mineralisation can occur, and substantial electrolyte wastage has been shown 24 h after BEA treatment (Sabatini *et al.*, 1981).

The presence of "MAP" based bladder calculi in 5 BEA-treated rats suggests that the induction of RPN (and perhaps the associated medullary matrix changes) can play a key role in the development of the crystalluria and calculi, but highlights those factors that could contribute to dissolution. The relevance of MAP crystals and calculi in this acute model in the rat to human analgesic abusers seems likely, since similar matrix changes have been described in patients (Gloor, 1978). In addition, electrolyte wastage could play a very significant role in these patients (Jaeger *et al.*, 1982) in the presence of recurrent bacterial infection (Dubach *et al.*, 1983; Eknoyan, 1984), which would increase urinary pH and allow MAP calculi to develop when the solubility product was exceeded.

There appear to be little published data on the formation of urinary MAP crystals *per se* and most inferences must be drawn from the massive body of literature on other urinary tract calculi. MAP is encountered relatively infrequently as the major component of urinary stones, although it is often associated with calcium oxalate and phosphate urolithiasis. MAP is, however, the major component of "staghorn" calculi which form in (and may block) the renal pelvis and cause progressive damage in analgesic abusers.

BEA treatment caused a crystalluria, which consisted of a magnesium ammonium potassium phosphate complex, within a few hours of administration. This suggests that changes in the medullary matrix (associated with the development of renal papillary necrosis) can play a major role in altering the electrolyte homeostasis of the medulla (Gregg *et al.*, 1990a,b). Interestingly, Tamm-Horsfall glycoprotein has a controversial role in the formation of urinary stones, where it has been suggested to be a crystal promoter (Hallson and Rose, 1979) and an inhibitor (Kitamura and Pak, 1982). We have shown that Tamm-Horsfall glycoprotein is released from the distal nephron during the course of a BEA-induced RPN (Bach and Bridges, 1985), another factor that may contribute to the formation of calculi.

There has been little attempt to delineate the contributory role of calcification of damaged tissue (Hare and Poynter, 1974; Burry *et al.*, 1977) from calcium wastage (Jaeger *et al.*, 1982) and recurrent urinary tract infection (Dubach *et al.*, 1983; Eknoyan, 1984) as the primary cause of the high incidence of renal calculi and bladder stones in the analgesic abuser (Gault *et al.*, 1968; Stewart, 1978; Kincaid-Smith, 1980).

The presence of calculi has generally been regarded as a late complicating factor of the analgesic abuse syndrome and there appears to be no published data on the chemical composition of the urolithiases. In fact, the induction of urinary tract infection in rats is much easier after a BEA-induced RPN (Thiele, 1974) and if analgesics are given concomitantly (Vivaldi, 1968). Similar matrix changes, together with electrolyte wastage, mineralisation and recurrent urinary tract infection in human analgesic abusers may be relevant to the development of urinary calculi in this population.

These investigations show the occurrence of magnesium ammonium phosphate bladder calculi in a small proportion of animals given an acute papillary necrosis with BEA. Monitoring of urine shortly after the administration of BEA showed a substantial but transient MAP crystalluria. The presence of acid soluble bi-refringent material in the medulla matrix, associated with loss of glycosaminoglycan staining, supports the concept of a super-saturation. The incidence of bladder calculi in this system is too low to be used as a model. The fall in urinary pH may play a prominent role in crystal dissolution and it is possible that the incidence of bladder calculi could be increased by alkalisation of the urine, dietary manipulation (including atherogenic feeds), electrolyte loading or manipulation, or experimental urinary tract infection.

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The Author

P. H. Bach, BSc(Hons), MSc, PhD, Senior Lecturer in Toxicology, Head, Nephrotoxicity Research Group.

Requests for reprints to: P. H. Bach, Nephrotoxicity Research Group, Robens Institute of Health and Safety, University of Surrey, Guildford, Surrey GU2 5XH.

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The Encased Ureter: Bullet and Bodkin Pattern, a Reliable Radiographic Sign

M. KUNIN and W. E. GOODWIN

Department of Radiology, Uroradiology Section, Harbor-UCLA Medical Center, Torrance; Department of Surgery, Division of Urology, UCLA School of Medicine, Los Angeles, USA

Summary—Among the causes of constricted ureter is benign or malignant encasement. The diagnosis of ureteric encasement is frequently overlooked, even by well informed clinicians and radiologists. The most common benign cause is retroperitoneal fibrosis and the most frequent malignant causes are extension from an adjacent primary tumour, true metastases to the ureter and lymphoma. Lack of recognition of the process may lead to mistaken diagnosis of an inflammatory stricture or infiltrating transitional cell tumour, with resultant inappropriate management. A sign which appears to be almost specific for encasement, the bullet and bodkin configuration, is described here. Newer imaging modalities such as computed tomography and ultrasound, while helpful, are probably less sensitive and less specific than the retrograde ureterogram because a detectable mass is not always present.

The radiological differential diagnosis of a constricted segment of ureter includes strictures of various aetiologies, infiltrating transitional cell carcinoma, encasement of the ureter, simple compression by an adjacent inflammatory or neoplastic mass, achalasia, retrocaval location, polyarteritis nodosa, notching due to collateral circulation, ureteric varices and normal variants such as a vascular crossing. These are some of the more frequent causes. Some manifestations of encasement of the ureter appear to be among the less commonly recognised lesions by knowledgeable clinicians and radiologists alike. In this report, encasement implies either that the ureter is surrounded by a constricting extraureteric mass or that the lumen is constricted by the presence of tumour cells, with or without fibrosis, in the wall of the ureter or in the surrounding periureteric tissues. A useful sign of encasement, probably almost pathognomonic, is the bullet and bodkin pattern (Figs 1–3).

The pattern consists of a dilated ureter interrupted by a constricted segment (Fig. 1). Proximal to the constriction, the ureter displays a rounded or snubnosed bullet-like configuration. The narrowed portion tapers rapidly like a cranially pointed dagger to meet the "bullet", from below. It is the fancied resemblance of the narrowed portion to a bodkin (a thick blunt needle, a dagger) that provides part of its name (Oxford English Dictionary, 1977).

Patients and Methods

The radiographs of 65 patients displaying ureteric encasement were analysed in an attempt to categorise the morphology. These patients were seen at Harbor-UCLA Medical Center over a 10-year period, supplemented by selected patients from the University of California Medical Center at Los Angeles during that time.

Results

A total of 16 patients displaying the bullet and bodkin pattern were found. In no case was the pattern observed in the absence of encasement. In 13 cases pathological proof was obtained. In 3 remaining cases a known primary carcinoma existed and a presumptive diagnosis of encasement due to metastasis was made. The Table summarises salient details.

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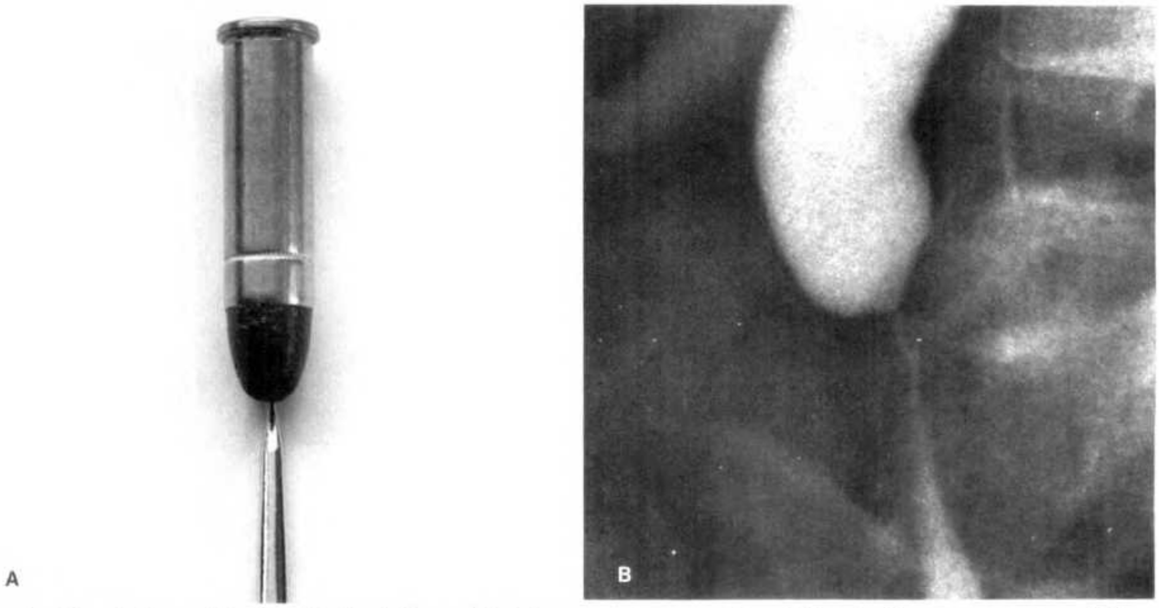

Fig. 1 (A) A bullet and bodkin. (B) The bullet and bodkin pattern in retroperitoneal fibrosis. Note ureterectasis and blunt configuration of ureter proximal to constriction, the "bullet". The narrowed portion, the "bodkin", characteristically tapers to a point where it joins the proximal dilated portion.

In most cases the intravenous urogram showed no renal excretion, or hydroureteronephrosis, sometimes with blunt termination of the ureter (Fig. 2). This finding in itself suggests encasement. The retrograde ureterogram was diagnostic.

Table Bullet and Bodkin Pattern in Encased Ureter

Patient no.	*Primary carcinoma*	*Other aetiology*	*Pathological confirmation*	*Known primary*
1	Endometrium		+	
2	Rectosigmoid		+	
3	Rectum		+	
4	Prostate		+	
5	Prostate		+	
6	Prostate		+	
7	Endometrium		+	
8		Retroperitoneal fibrosis	+	
9		Retroperitoneal fibrosis	+	
10		Retroperitoneal fibrosis	+	
11		Retroperitoneal fibrosis	+	
12		Retroperitoneal fibrosis	+	
13		Tubo-ovarian abscess	+	
14	Colon			+
15	Prostate			+
16	Cervix			+

Benign 6/16. Malignant 10/16.
Retroperitoneal fibrosis 5/16.

Discussion

It may be argued that a computed tomographic study is diagnostic and less invasive than retrograde study. It is true that such an examination is helpful in delineating the extent of a mass lesion (Ambos *et al.*, 1979; Bosniak *et al.*, 1982). However, Brun *et al.* (1981) reported that in 8 of 23 cases of retroperitoneal fibrosis the fibrosis was not visible on computed tomography. Others have found that computed tomography has a sensitivity of 50% or less in detecting local extension of tumour or metastases from prostatic cancer (Emory *et al.*, 1983; Platt *et al.*, 1987). Cohen *et al.* (1974) reported 31 cases of ureteric metastases. They included only malignancies involving growth within the wall of the ureter and those which showed the presence of tumour in the immediate periureteric lymphatics and tissues, specifically excluding extension from an adjacent malignancy. (No such restrictions were placed on the material included in this report). They found 2 basic patterns. The most common, occurring in 19 of 31 cases (61%) was involvement of all layers of the ureteric wall by constricting metastases. The next most common pattern was periureteric soft tissue infiltration by tumour with

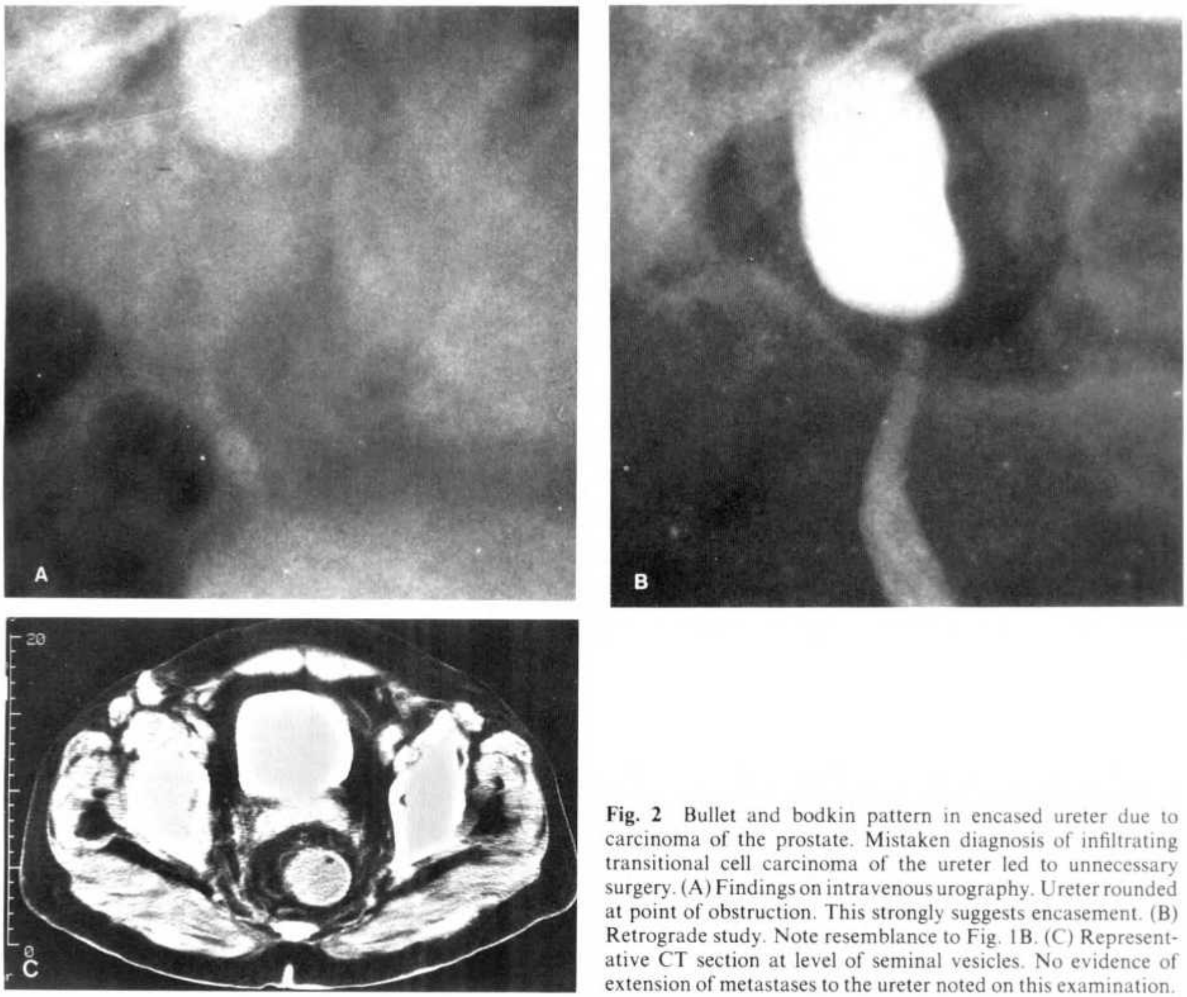

Fig. 2 Bullet and bodkin pattern in encased ureter due to carcinoma of the prostate. Mistaken diagnosis of infiltrating transitional cell carcinoma of the ureter led to unnecessary surgery. (A) Findings on intravenous urography. Ureter rounded at point of obstruction. This strongly suggests encasement. (B) Retrograde study. Note resemblance to Fig. 1B. (C) Representative CT section at level of seminal vesicles. No evidence of extension of metastases to the ureter noted on this examination.

concentric compression of the ureteric lumen in 11 cases (35%).

It is clear that most such ureteric metastases would be unlikely to show evidence of encasement by computed tomography. This suggests that a retrograde ureterogram, by demonstration of compression of the ureteric lumen, is more sensitive for diagnosis of encasement than CT or other imaging modalities.

The most frequent causes of encasement of the ureter are metastatic malignancy and extension from an adjacent malignancy, lymphoma and retroperitoneal fibrosis. Of these, malignancy is, in our experience, the most common (Kunin, unpublished data). Other differential diagnostic considerations include endometriosis, abscess and Crohn's disease involving the retroperitoneum.

In this series of 65 cases of ureteric encasement, most patients with a malignant primary tumour did not present *de novo* with this manifestation (Kunin, unpublished data). In most cases the primary tumour was already known at the time of discovery of encasement of the ureter. This accords with previous reports indicating that widespread metastases were already present in 90% or more of such patients (Cohen *et al.*, 1974; Richie *et al.*, 1979).

This is not invariably true. At times, recognition of the bullet and bodkin pattern is the only clue to the ultimate diagnosis.

In at least 4 previous reports of ureteric obstruction, the bullet and bodkin configuration was illustrated: (1) the exposition on computed tomography of ureteric obstruction by Bosniak *et al.* (1982), (2) the report by Kaufman (1962) of unusual causes of extrinsic ureteric obstruction, (3) the study by Friedenberg *et al.* (1966) on the clinical significance of ureteric deviations and (4) the description of ureteric metastases via lymphatics in

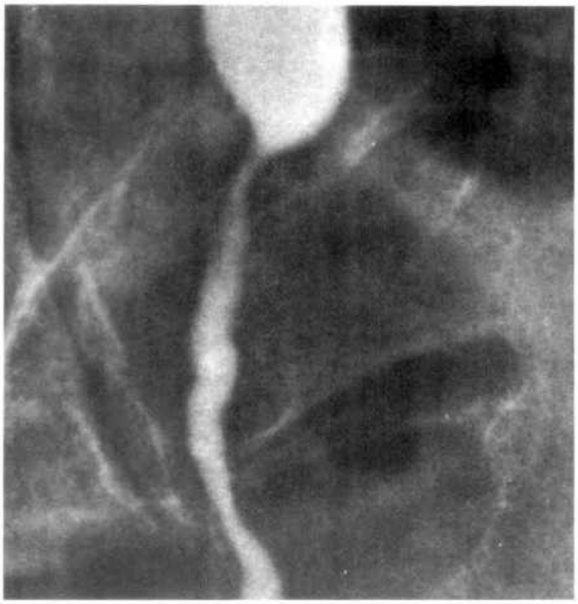

Fig. 3 Bullet and bodkin configuration observed in retroperitoneal metastatic carcinoma of the breast.

carcinoma of the prostate by Campbell and Aldis (1980). However, in no instance was the pattern reported to be specific or even suggestive for the diagnosis of encasement.

While the bullet and bodkin pattern was observed only in the presence of ureteric encasement, it is by no means the only manifestation of this condition. Further discussion of the topic is beyond the scope of this report.

In summary, the presence of a bullet and bodkin pattern is helpful in the differential diagnosis of a constricting ureteric lesion.

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The Authors

M. Kunin, MD, Clinical Professor of Radiology, School of Medicine, University of California at Los Angeles; Chief, Uroradiology, Harbor-UCLA Medical Center.

W. E. Goodwin, MD, FACS, FAAP, Emeritus Professor of Surgery-Urology, School of Medicine, University of California at Los Angeles.

Requests for reprints to: M. Kunin, Harbor-UCLA Medical Center, Department of Radiology, Uroradiology Section, Box 27, 1000 West Carson Street, Torrance, California 90509, USA.

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Bladder Function in the Mentally Retarded

P. A. HELLSTRÖM, MARJO-RIITTA JARVELIN, M. J. KONTTURI and N.-P. HUTTUNEN

Department of Surgery, Oulu University Central Hospital; Tahkokangas Central Institution for the Mentally Retarded, Oulu; Paediatric Unit, Central Hospital of Central Finland, Jyväskylä, Finland

Summary—A group of 21 mentally retarded patients with severe, long-standing urinary symptoms underwent urodynamical investigation. The most common abnormalities were detrusor areflexia and detrusor hyper-reflexia. Of 11 patients treated surgically, 10 derived marked benefit. Drugs were successful in reducing micturition problems in 3/6 patients. Severely retarded patients with spastic quadriplegia are difficult to investigate and if this is associated with detrusor hyper-reflexia it is impossible to treat them in any way. Severely retarded patients with detrusor areflexia and infrequent voiding can benefit from bladder outlet surgery. Patients with moderate (especially mild) retardation can be investigated and treated in the same way as non-retarded people.

Mental retardation encompasses a heterogeneous group of disorders and those affected are seldom handicapped by deficient intelligence alone (Gustavson *et al.*, 1977; Mitchell and Woodthorpe, 1981). According to the Finnish Registrar of the Mentally Handicapped (1986), approximately 25% of all mentally subnormal people in Finland had cerebral palsy or other difficulties in movement, 20% had epilepsy, and functional speech defects and disorders of the senses were common. Urinary incontinence and nocturnal enuresis also occur more often in mentally retarded people than in the normal population (Thorne, 1944; Reid *et al.*, 1978; Mitchell and Woodthorpe, 1981; Järvelin *et al.*, 1988). Our knowledge of the cause and character of urinary disorders in the mentally retarded is limited, however. McNeal *et al.* (1983) investigated a group of cerebral palsied patients, excluding those with intelligence quotients <40, and a total of 13 received cystometrograms. Decter *et al.* (1987) performed urodynamic tests on children with cerebral palsy, some of whom were also mentally retarded, and found that more than one-third had symptoms of dysfunctional voiding.

We have examined a selected group of mentally retarded adults urodynamically in order to characterise the nature of their urinary disorders.

Patients and Methods

The series comprised 21 mentally retarded patients (16 men and 5 women) referred for examination because of long-standing urinary problems and difficulties in nursing. Their mean age was 36 years (range 18–69). Their levels of mental retardation, associated handicaps or diseases and urinary symptoms are listed in the Table.

Incontinence is taken to mean involuntary loss of urine during the day or during both day and night, while wetting only during sleep is designated nocturnal enuresis. Otherwise we have followed the terminology of the International Continence Society (1988).

The aetiology of the mental retardation, if known, is indicated in the Table. The most difficult patients were those with spastic quadriplegia, who were all unable to walk. The most common urinary symptoms were incontinence, nocturnal enuresis and urinary retention/poor bladder emptying. All patients underwent urodynamic investigation, including medium-fill water cystometry, pressure-flow electromyography and urethral pressure profilometry. The methods, definitions and units conformed to the standards recommended by the International Continence Society (1988). In 10 of the 17 patients who received some form of treatment the result was verified in a control examination (including maxi-

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Table Clinical Features, Urodynamic Findings and Treatment

Age (years)	*Sex*	*Level of MR*	*Associated handicaps/ Aetiology*	*Symptoms*	*Urodynamics*	*Treatment*
22	M	Profound	Spastic quadriplegia, Cerebral bleeding	Urinary retention UTI	Detrusor areflexia, BC > 1000 ml	BNI
19	M	Profound	Spastic quadriplegia epilepsy, PA	Epididymitis, incontinence	BC 500 ml, residual 150 ml	None
30	M	Profound	Spastic quadriplegia	Incontinence	Detrusor hyper-reflexia	None
30	M	Profound	Spastic quadriplegia, PA	Incontinence	Detrusor hyper-reflexia	None
45	M	Mild	Spastic quadriplegia	Urinary retention	Detrusor areflexia	BNI
25	M	Severe	Spastic quadriplegia, epilepsy	Urinary retention, incontinence, UTI	Detrusor areflexia, BC > 1000 ml	BNI
41	M	Severe	Spastic quadriplegia	Incontinence	Normal	Desmopressin
29	M	Severe	Spastic quadriplegia, PA	Urinary retention, UTI	High micturition pressure	BNI
18	M	Mild	Spastic hemiplegia	Nocturnal enuresis, increased frequency	Detrusor hyper-reflexia	Anticholinergics
19	M	Mild	Spastic diplegia, epilepsy, PA, immaturity	Incontinence, poor stream, retention, increased frequency	Detrusor hyper-reflexia/high micturition pressure	BNI/sphincterotomy
25	M	Profound	Down's syndrome	Incontinence, poor stream	High micturition pressure, BC > 1000 ml	BNI
40	M	Severe	Ullrich-Noonan's syndrome	Poor emptying, increased frequency	Detrusor areflexia	BNI/TURP
61	M	Moderate		UTI	Detrusor areflexia	BNI
49	M	Severe	Xeroderma pigmentosum, epilepsy	Abdominal distension	Poor flow, residual 640 ml	BNI/reduction cystoplasty
50	M	Moderate		Urinary infections	Poor flow, residual 310 ml	BNI
34	M	Mild		Post-mictional dribbling	Normal	None
43	F	Moderate		Stress incontinence	Normal	Phenylpropanolamine
21	F	Mild		Nocturnal enuresis	Normal	Anticholinergics
39	F	Severe		Increased frequency	Detrusor hyper-reflexia	Anticholinergics
39	F	Mild		Stress incontinence	Detrusor areflexia	Phenylpropanolamine
69	F	Mild		Hydronephrosis, infections	Detrusor areflexia, residual 500 ml	BNI

MR = mental retardation, BC = bladder capacity, BNI = bladder neck incision, PA = perinatal asphyxia, UTI = urinary tract infection, TURP = transurethral resection of prostate.

mum flow rate and residual urine measurement) and in 7 cases a questionnaire was used.

Results

It was possible to perform the urodynamic examination in all cases. Thirteen patients micturated during the pressure-flow examination, but 8 were unable to do so. The principal urodynamic findings are depicted in the Table. They included detrusor areflexia, detrusor hyper-reflexia, high micturition pressure and large bladder capacity. The findings were almost normal in 4 cases. The 8 patients with spastic quadriplegia had poor bladder emptying associated with detrusor areflexia in 3/4 cases, incontinence being associated hyper-reflexia in 2 and with almost normal findings in a further 2 cases.

Case report

A 49-year-old man was referred to the Department of Internal Medicine with abdominal distension thought to be due to ascites. A puncture yielded 6400 ml clear fluid which was suspected on analysis to be urine. The patient was catheterised and 3800 ml residual urine obtained. The catheter was left in place for several weeks Urodynamic examination 1 day after withdrawal of the catheter revealed 650 ml residual urine. There was no rise in bladder pressure after filling with 900 ml at cystometry, but the maximum detrusor pressure in the pressure-flow examination was 27 cm of water. The patient underwent bladder neck incision, with poor results, but later a reduction cystoplasty was performed with excellent results, so that 6 months post-operatively there was no residual urine.

The treatments given to the various patients are listed in the Table. Surgery was tried in 11 cases, no treatment was recommended in 4, and medication was the only treatment in 6.

The most common operation was bladder neck incision (BNI), which was performed on 11 patients and led to an improvement in bladder emptying in 8 (73%) (7 men and 1 woman). Transurethral resection of the prostate failed to restore micturition after unsuccessful BNI in 1 patient, reduction cystoplasty was the solution for the problem in another, and external sphincterotomy was helpful in a third case. Surgery was helpful in 10/11 cases (91%).

Two women with stress incontinence were dry after phenylpropanolamine treatment. Anticholinergics (emepronium carragenate) were helpful for 1 woman among the 3 patients with detrusor hyper-reflexia mainly treated by medication. Desmopressin failed to cure nocturnal enuresis in 1 patient, largely due to application problems. Medication was beneficial in 3/6 patients.

Discussion

The present series appears to be the first in which urodynamics have been systematically used to evaluate mentally retarded patients. Those with severe mental retardation are difficult to examine as they cannot co-operate. This is one reason for the few publications on this subject. Another may be the belief that it is not possible to help these people at all.

Although cerebral palsy is regarded as a cause of neurogenic bladder dysfunction (Cass and Geist, 1972; Waldbaum and Muecke, 1972), the nature of bladder function cannot be evaluated according to the level of the lesion alone (Light *et al.*, 1984). Our patients with spastic quadriplegia could have had either detrusor areflexia or detrusor hyper-reflexia, but the symptoms were nevertheless often consistent with the urodynamic findings, retention being associated with detrusor areflexia and incontinence with detrusor hyper-reflexia. Although all 4 patients with spastic quadriplegia and urinary retention or infrequent voiding derived benefit from bladder outlet surgery, numerous technical and practical problems are associated with the examination and treatment of these patients.

It was concluded that moderately and mildly retarded patients without serious neurological defects can be investigated in the same way as non-retarded patients and the treatment (surgery/drugs) can be chosen according to the urodynamic findings. The fact that 91% of surgically treated patients benefited from the operation is promising. Bladder neck incision can reduce bladder outlet resistance and improve bladder emptying in some mentally retarded patients. Apart from patients with high micturition pressure, those with detrusor areflexia are also candidates for this operation and in this group there was no record of incontinence becoming worse after the procedure. Bladder neck incision is not helpful in patients with detrusor hyper-reflexia. Reduction cystoplasty is the operation of choice in selected cases. As shown in the present study and also by Kinn (1985), these large capacity bladders can show detrusor contraction and emptying may be excellent post-operatively.

Anticholinergics have been shown to be beneficial in neurogenic bladders caused by cerebral palsy (McNeal *et al.*, 1983; Decter *et al.*, 1987) but the present series contained only 1 such case. An encouraging finding was the total cure of stress incontinence in 2 women using alpha-sympathomimetic phenylpropanolamine.

Our patients were highly selected, and most mentally retarded patients with enuresis, especially if institutionalised, are best treated by positive encouragement to achieve continence, nightly awakening and restriction of fluids before bedtime (Phibbs and Wells, 1982). Some mentally retarded people with bladder dysfunction, however, should be examined urodynamically and treated. Although most will fail to become completely asymptomatic, nursing will be easier and institutionalisation may be avoided in some cases.

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The Authors

P. A. Hellström, MD, PhD, Urologist, Oulu University Central Hospital.

Marjo-Riitta Jarvelin, MD, PhD, Paediatrician, Tahkokangas Central Institution for the Mentally Retarded.

M. J. Kontturi, MD, PhD, Professor, Head of Division of Urology, Oulu University Central Hospital.

N -P Huttunen, MD, PhD, Paediatrician, Head of Paediatric Unit of Central Hospital of Central Finland.

Requests for reprints to: P. A. Hellström, Division of Urology, Department of Surgery, Oulu University Central Hospital, SF-90220 Oulu, Finland.

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Oxybutynin Hydrochloride (3 mg) in the Treatment of Women with Idiopathic Detrusor Instability

KATE H. MOORE, D. M. HAY, A. E. IMRIE, A. WATSON and M. GOLDSTEIN

Department of Gynaecology, Princess Royal Hospital, Hull; Department of Statistics, University of Hull

Summary—Oxybutynin hydrochloride (3 mg) was compared with placebo by randomised, double-blind crossover trial in 53 females with idiopathic detrusor instability. Symptoms were cured or markedly improved in 60% of patients on oxybutynin and 2.3% on placebo. During the first treatment period, oxybutynin reduced the frequency of voiding by 35%, compared with 9% for placebo. Oxybutynin gave a significantly greater improvement than placebo in volume at the first desire to void (70 ml increase versus 7.7 ml), maximum filling-phase detrusor pressure (17 cm H_2O reduction versus no benefit) and cystometric capacity (104 ml increase versus 7.0 ml). A marked oxybutynin carry-over effect was seen during the second treatment period.

Side effects from the 3 mg dose of oxybutynin caused 7.5% of subjects to discontinue therapy.

Idiopathic detrusor instability is a socially incapacitating disorder which remains difficult to treat despite the numerous therapeutic regimes which are available. Various drugs, such as flavoxate hydrochloride (Jarvis, 1981), emepronium bromide (Meyhoff *et al.*, 1983), imipramine (Castleden *et al.*, 1986) and the latest agent teroline (Tapp *et al.*, 1987; Andersen *et al.*, 1988), have all been employed with limited success.

Oxybutynin hydrochloride is an anticholinergic agent with local anaesthetic properties (Diokno and Lapides, 1972). The 5 mg tablet has been available on a "named patient basis" in Great Britain for over a decade. Only 2 small placebo-controlled trials using oxybutynin for treatment of idiopathic detrusor instability have been carried out in this country. Moisey *et al.* (1980) reported symptomatic improvement in 9 of 12 patients, with urodynamic improvement in 5. Cardozo *et al.* (1987) reported that oxybutynin significantly reduced the mean maximum detrusor pressure of the 23 post-menopausal women who completed the trial, at the expense of increased residual urine volume. Both studies found a high incidence of side effects for the 5 mg dose, causing 18 and 21.6% of patients respectively to discontinue treatment.

We aimed to measure the efficacy and severity of side effects using a lower dose tablet (oxybutynin 3 mg) in the treatment of idiopathic detrusor instability.

Patients and Methods

A total of 53 women entered the study, following referral by a urologist or gynaecologist for urodynamic investigation. Neurological and other urological disorders were excluded by history, physical examination and culture of midstream urine. Medium-fill subtraction cystometry and uroflowmetry defined idiopathic detrusor instability in all subjects.

Patients with coexistent genuine stress incontinence, low compliance bladder, bacterial or interstitial cystitis, age greater than 75 years or previous treatment with oxybutynin were excluded. Only patients with involuntary detrusor contractions >30 cm H_2O during the filling phase of cystometry were recruited (because it was our usual practice to reserve oxybutynin therapy for patients with marked instability). All who fulfilled these criteria during an 18-month recruitment period were invited

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to join the trial, which was approved by the local Ethics Committee. Two patients refused (1 for geographical reasons; the other found cystometry too unpleasant).

Patients completed a baseline frequency-volume chart (FVC) for 3 days and were then randomly allocated to treatment with oxybutynin 3 mg *tid* (Group X, N=28) or placebo (Group Y, N=25). Randomisation of patients was stratified according to the magnitude of the observed detrusor contractions (moderate instability=detrusor contractions 30–59 cm H_2O, severe >60 cm H_2O), so that severely affected patients would be equally distributed into both arms of the trial. Tablets were packaged into random-table pairs by the manufacturer (Levias Pharmaceuticals, Finland); the code was held by the hospital pharmacist. At recruitment, patients received a single-page explanation about the nature of detrusor instability and basic principles of bladder training, but no specific retraining programme was employed.

After the first treatment period, symptomatic improvement was recorded (marked, good, fair, or nil benefit for urgency and urge incontinence). Side effects were documented by visual analogue score for the symptom of dry mouth (scale 1–10) and by a general questionnaire. FVC and urodynamic studies were repeated. Following a 1-month wash-out period, patients completed another FVC and then crossed over to the second-period tablet. The third cystometry was repeated by the same observer (KHM) and the fourth frequency-volume chart was collected.

Each treatment bottle contained a 2-week surplus of tablets; a tally of returned tablets correlated well with patients' self-reported compliance. Comparative drug efficacy was measured using 2-tailed *t* test ($P=0.05$). Methods, definitions and units conform to the standards recommended by the International Continence Society (1988) except where specifically stated.

Long-term follow-up

All patients were offered follow-up by the initial observer at 2-monthly intervals. During these appointments, frequency-voiding charts were discussed and specific bladder training advice was given. Follow-up continued until symptomatic improvement allowed a return to normal life style with no more than 8 voids/day on FVC; the maximum duration of follow-up was 18 months.

Results

Patients in each arm of the trial were similar with regard to age, parity, duration of symptoms, frequency of micturition and urodynamic parameters (Table 1).

During the first treatment period, 1 patient on oxybutynin and 3 patients on placebo dropped out for personal reasons; their results were excluded from all analysis. At the end of the first treatment period, 3 patients found oxybutynin so unpleasant that they wished no further treatment, leaving 24 patients to enter the wash-out period, when a further 3 dropped out. All 22 patients who began with placebo continued to participate despite placebo side effects (1 patient subsequently found the research study too inconvenient). Of the 11 patients who dropped out, 4 (7.5% of 53 subjects) cited oxybutynin side effects as their reason (Table 2).

Assessment of drug efficacy by subjective opinion

Of the 27 patients who initially received oxybutynin, 15 (55%) noted symptomatic cure (5) or

Table 1 Characteristics of Patients at Entry to Trial

	Group X Oxybutynin first (N=27) Mean (SD)	*Group Y Placebo first (N=22) Mean (SD)*	*All Patients Mean (SD)*
Age (years)	46.0 (11.7)	46.4 (12.4)	46.2 (12)
Parity	2.3	2.2	2.2
Duration (years)	7.5 (7.9)	8.9 (9.0)	8.2 (8.5)
Voids/day	11.1 (7.9)	12.1 (5.7)	11.6 (6.9)
Residual volume (ml)	23.1 (34)	22.7 (34)	22.9 (34)
First desire to void (ml)	94.2 (66)	107.4 (101)	100.4 (84)
Maximum detrusor filling pressure (cm H_2O)	55.3 (23)	59.2 (26)	57.5 (25)
Maximum cystometric capacity (ml)	275 (164)	290 (168)	282 (166)

Table 2 Reasons for Leaving Trial

Intolerable side effects	4
Intervening medical illness	2
Decision not to participate in research trial	2
Acute marital breakup	3
Total	11

marked improvement (10), versus marked improvement for 1 of 21 who crossed over to placebo. In the placebo-first group, 1 patient noted marked improvement; after crossover to oxybutynin, 14 of 21 patients (67%) noted cure (6) or marked improvement (8). Overall, 60% of patients on oxybutynin experienced cure or marked improvement versus 2% for placebo (Fig. 1).

Assessment of drug efficacy by frequency/volume charts

Frequency of micturition during initial oxybutynin therapy was reduced from 11.2 to 7.3 voids/day (35% benefit); the drug effect appeared to persist during wash-out (8.0 voids/day) and placebo periods (8.3 voids/day). For the placebo-first group, frequency improved from 12.0 to 10.9 voids/day (9% placebo effect), changed little during wash-out (10.3 voids/day) and then improved to 8.5 voids/day on oxybutynin (29% benefit with respect to baseline, 17% with respect to wash-out). Some patients did not complete every FVC, but data from subjects completing all 4 charts showed the same trend (Fig. 2).

Cystometry results after first treatment period

Because the frequency/volume chart data had suggested a drug carry-over effect, we analysed the urodynamic data using 2 methods. Firstly, cystometric changes for both of the first treatment periods were compared. Secondly, the changes during the crossover trial were studied.

Comparing results for both of the first-treatment periods, the efficacy of oxybutynin was significantly greater than that of placebo for increased volume at first desire to void ($P=0.02$), reduced maximum detrusor pressure ($P=0.02$) and increased maximum cystometric capacity ($P=0.006$) (Table 3).

Cystometry revealed a stable bladder in 6 patients on oxybutynin (22%) and >50% improvement in

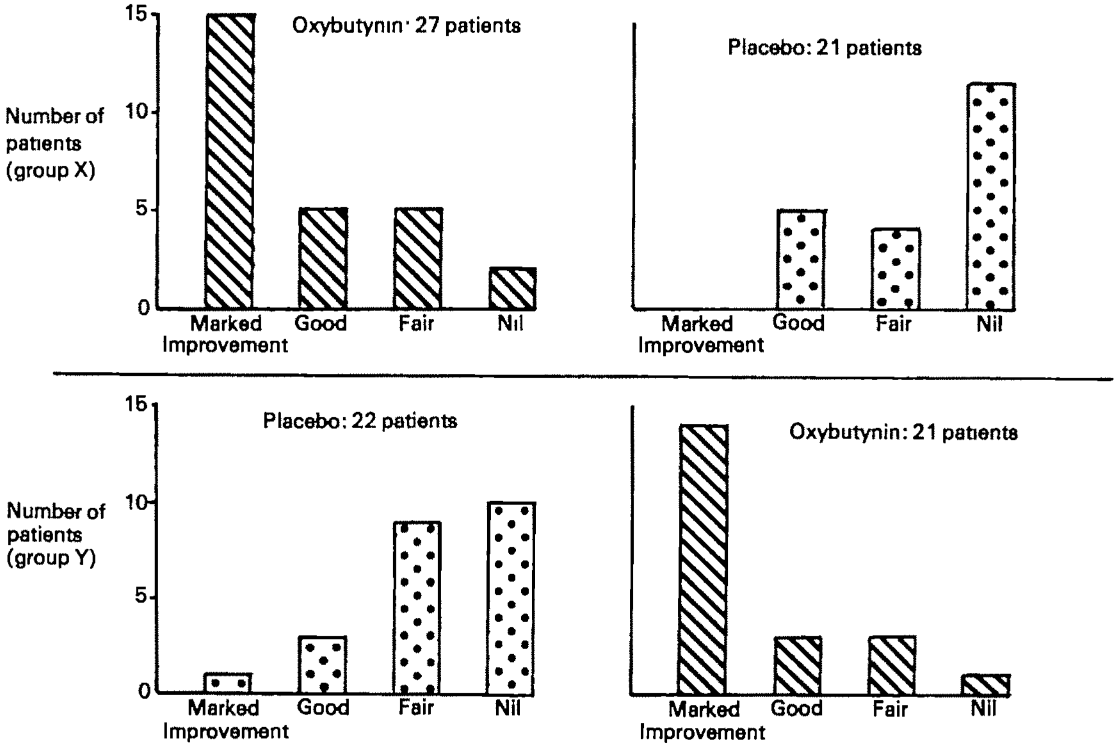

Fig. 1 Treatment response: subjective opinion.

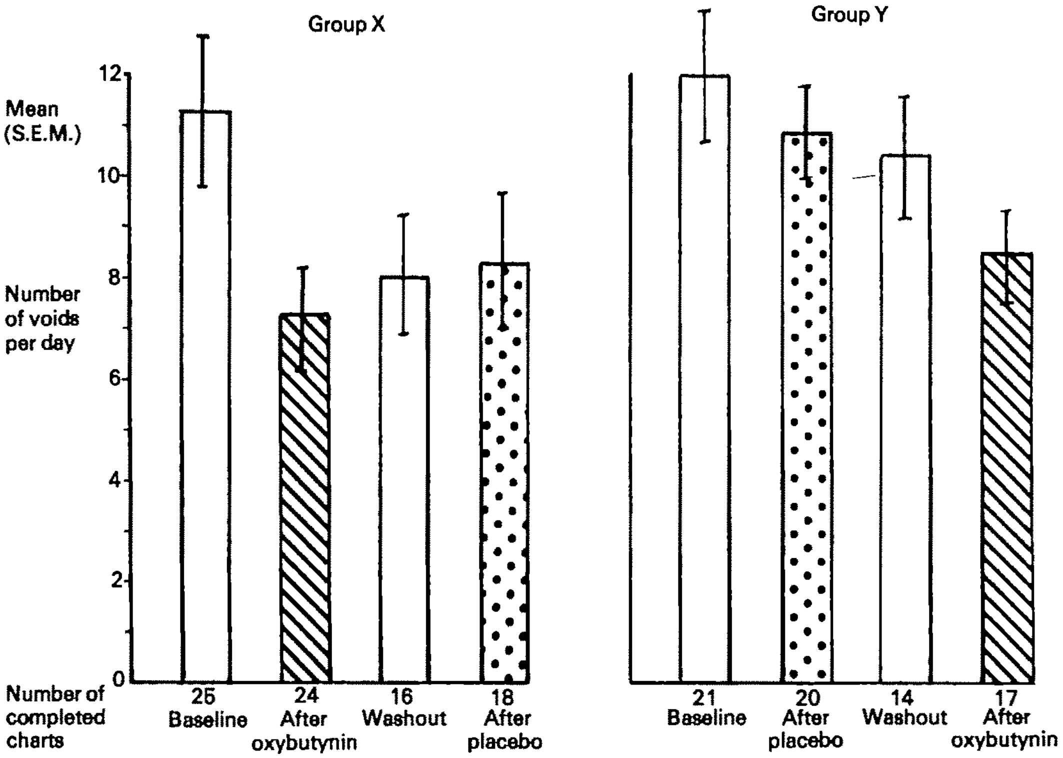

Fig. 2 Treatment response: frequency volume charts.

detrusor pressure in 13 patients (48%). After placebo, 1 stable bladder (4.5%) and >50% improvement in 5 patients (23%) occurred.

Cystometry results for crossover trial

After initial oxybutynin therapy, bladder volume at first desire to void (FDV) increased from baseline of 94 ml (SD 66) to 164 ml (SD 103). Despite a 1-month wash-out period, the treatment effect appeared to carry over into the placebo period (improvement to 186 ml, SD ± 100) (Fig. 3).

For the placebo-first group, volume at FDV (baseline 107 ml, SD ± 101) changed little after placebo (115 ml, SD ± 76); a major improvement was seen after oxybutynin (161 ml, SD ± 102); this did not reach statistical significance ($P = 0.11$) largely because of the wide variation seen in a single unusual patient. The volume at FDV for women receiving placebo-first and placebo-second was significantly different ($P = 0.03$), suggesting an oxybutynin carry-over effect.

Similar trends were seen for changes in maximum detrusor pressure and maximum cystometric capacity (Figs 4 and 5).

Effect of oxybutynin on residual urine volume

Although oxybutynin tended to increase residual urine volume, this trend was not significantly

Table 3 Urodynamic Results after First Treatment Period

	Change in volume at first desire to void Mean (SD)	*Change in maximum detrusor pressure Mean (SD)*	*Change in maximum capacity Mean (SD)*
Drug A = Oxybutynin (N = 27)	+70.0 (103)	−16.9 (19.5)	+104.0 (131)
Drug A = Placebo (N = 22)	+7.7 (76)	+1.0 (28.7)	+7.0 (103)
	$P = 0.02$	$P = 0.02$	$P = 0.006$
95% confidence intervals	(10, 113)	(−32.5, −3.2)	(29, 165)

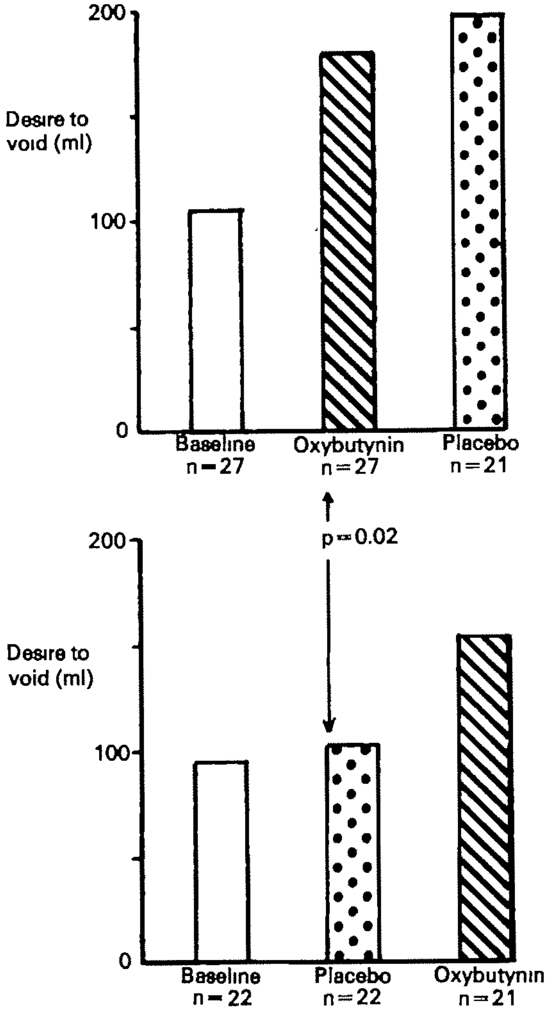

Fig. 3 Treatment response: bladder volume at first desire to void

different from the increase occurring after placebo therapy (Table 4).

Side effects

The mean visual analogue score for dry mouth noted during oxybutynin therapy was 6.26, versus 2.23 for placebo. Four patients found dry mouth so unpleasant that they discontinued the trial. Numerous other side effects were noted during placebo and oxybutynin treatments (Table 5).

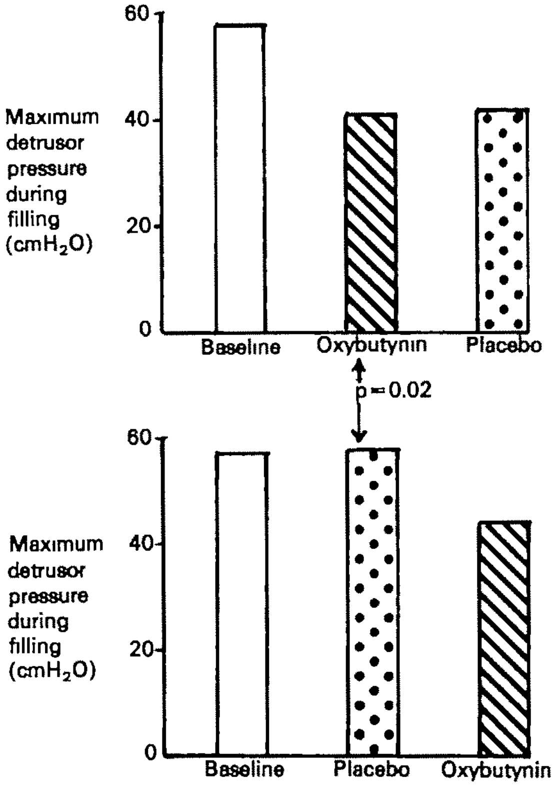

Fig. 4 Treatment response. maximum detrusor pressure.

Follow-up results

Of 42 patients completing the trial, long-term follow-up revealed that 12 were cured and had been able to cease medication; 14 showed marked improvement, allowing a normal life style despite some episodes of urgency/frequency, and 5 noted moderate benefit. Four found little or no benefit but continued follow-up; 3 patients changed to other medication and 3 failed to attend (Table 6).

Table 4 Changes in Residual Urine Volume

	Baseline Mean (SD)	*Change after Drug A Mean (SD)*		*Change after Drug B Mean (SD)*	
Group X	23.1 (34.2)	Oxybutynin	+22.4 (79.3)	Placebo	+10.0 (27.1)
Group Y	22.7 (34.0)	Placebo	+7.7 (45.7)	Oxybutynin	+25.7 (55.6)
		$P=0.42$		$P=0.33$	

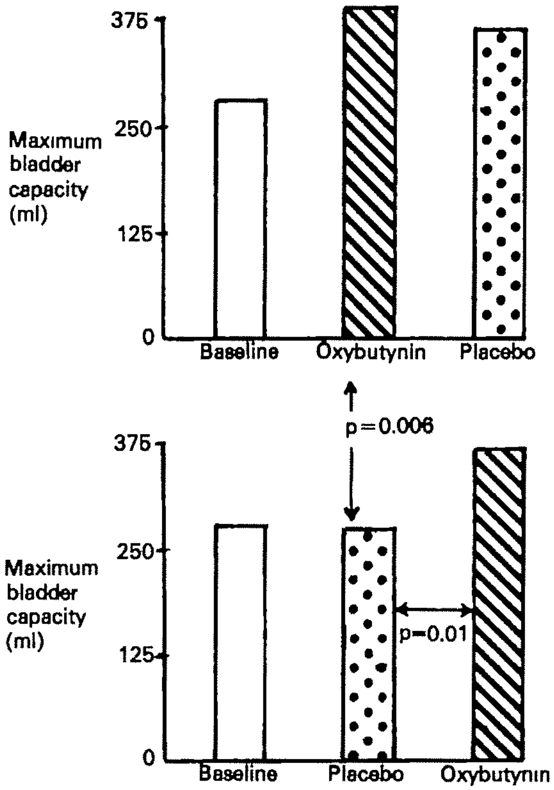

Fig. 5 Treatment response: maximum bladder capacity.

Discussion

This study of 49 female patients, all of whom appeared markedly affected by idiopathic detrusor instability, showed oxybutynin to be more effective than placebo as judged by symptomatic improvement, diminished frequency of voiding on FVC and all cystometric parameters. Anticholinergic side effects were frequently experienced during oxybutynin therapy but caused only 7.5% of patients to abandon treatment; placebo side effects occurred in 33%. The volume of residual urine was not significantly increased by oxybutynin treatment with respect to placebo.

Table 5 Side Effects on Oxybutynin and Placebo (%)

	Oxybutynin (N=48)	*Placebo (N=43)*
Dry mouth	88	33
Mouth ulcers	16	0
Constipation	12.5	0
Drowsiness	12.5	7
Nausea	8.3	2.3
Initial hesitancy	4.2	2.3
Dizziness	4.2	7.0
Metallic taste	2.4	2.3

Table 6 Results of Long-term Follow-up

Result	*No. of Patients*	*Mean duration of follow-up (months)*	*Range*
Cured, no treatment	12	5.2	2–10
Cured, on treatment	1	4.0	4
Marked benefit, no treatment	6	7.5	3–14
Marked benefit, on treatment	8	7.4	3–15
Moderate benefit, on treatment	5	13.0	5–18
Little or no help	4	9.0	3–18
Changed therapy	3	9.0	5–12
Lost to follow-up	3	0	0
Total	42	6.9	0–18

Our findings showed greater overall benefit and fewer side effects for oxybutynin in comparison with earlier studies. This may be partly due to the larger number of patients enrolled and use of the 3 mg dose respectively.

The prolonged benefit seen after oxybutynin therapy in the present study might be explained if the completion of 4 frequency-volume charts constituted a form of bladder training in its own right. If so, then more emphasis could be placed upon such patient self-monitoring in everyday clinical practice. The explanation may also lie in the fact that patients saw the same clinician at every visit, which may have improved their motivation to persist with treatment.

Aitchison *et al.* (1989) drew attention to the short-term unsustained response which may be seen in detrusor instability and to a 45% failed attendance rate during a 5-year retrospective survey. Millard and Oldenburg (1983) showed that motivation is an important prognostic feature in the treatment of idiopathic detrusor instability. Given the socially debilitating nature of detrusor instability symptoms and the demands made upon out-patient resources by patients with persistent symptoms, perhaps greater continuity of care could be provided if this results in an improved response to treatment.

The oxybutynin carry-over effect was detected because data for the 2 treatment arms were analysed separately. For ethical reasons we did not repeat cystometry after the wash-out period. However, the urodynamic findings in patients receiving placebo first differed significantly from those in patients receiving placebo second, and provide supportive evidence of a carry-over effect which is in agreement with the frequency-volume chart data. The statistical implications of such a period interaction are fully discussed in the literature on cross-over trials (Grizzle, 1965; Hills and Armitage, 1979). This methodological difficulty has been reported by Hellstrom *et al.* (1989) in a trial employing terodiline for childhood detrusor instability, but their study did not contain a wash-out period between the 2 treatments.

As a result of the carry-over effect seen in our study, the validity of performing cross-over trials for pharmacological treatment of idiopathic detrusor instability may be open to question, despite the larger numbers of participants required to give adequate statistical power to the simple parallel-treatment protocol.

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The Authors

Kate H. Moore, MRCOG, MRACOG, formerly Registrar, Department of Gynaecology, Princess Royal Hospital, Hull. Now Lecturer, Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, University of Liverpool.

D. M. Hay, FRCOG, Consultant Gynaecologist, Princess Royal Hospital.

A H. Imrie, FRCOG, Consultant Gynaecologist, Princess Royal Hospital.

A. Watson, MRCOG, Registrar in Obstetrics and Gynaecology, Princess Royal Hospital.

M. Goldstein, DPhil, Reader, Department of Statistics, University of Hull.

Requests for reprints to: Kate H Moore, University Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

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Response to Treatment of Detrusor Instability in Relation to Psychoneurotic Status

KATE H. MOORE and J. R. SUTHERST

Departments of Gynaecology, Princess Royal Hospital, Hull, and Arrowe Park Hospital, Upton, Wirral

Summary—A total of 53 females who entered a double-blind crossover trial of oxybutynin and placebo for idiopathic detrusor instability were questioned about life events and associated medical disorders and were given a psychometric test. Their response to treatment was studied in relation to these factors.

It was found that 11% of patients had nocturnal enuresis beyond age 8 and 25% had irritable bowel syndrome: their response to treatment was generally poor. Life events were not consistently related to treatment response. The mean psychoneurotic score of "poor responders" (43.7) was similar to that of female psychoneurotic out-patients (47.7), although one-third of poor responders were normal. Patients who responded well to simple anticholinergic treatment had a mean score (30.7), which was similar to that of normal urban females (33.5).

Most good responders and one-third of poor responders showed little evidence of psychoneuroticism: a further search for neurophysiological abnormality in idiopathic detrusor instability is needed.

Several studies have implicated psychological factors in the aetiology of idiopathic detrusor instability, but the evidence to support a causal relationship remains unclear. Early studies featured largely anecdotal evidence (Straub *et al.*, 1949; Jeffcoate and Francis, 1966; Frewen, 1978). Following the introduction of formal psychometric testing, 3 studies concluded that patients with detrusor instability were more neurotic than those with genuine stress incontinence (Crisp and Sutherst, 1983; Pierson *et al.*, 1985; Macauley *et al.*, 1987). A further large study found no significant difference between these groups of patients (Morrison *et al.*, 1986).

If detrusor instability is caused by psychological disturbance, one might postulate that severely neurotic patients will be difficult to treat. However, a correlation between the degree of psychoneuroticism and response to treatment has not been clearly shown (Hafner *et al.*, 1977; Millard and Oldenburg, 1983; Ferrie *et al.*, 1984).

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In this study, patients participating in a double-blind placebo-controlled crossover trial of oxybutynin (Moore *et al.*, 1990) were questioned about life events at the onset of urinary symptons, and were given a psychometric test. Our aim was to study whether the psychological attributes of poor responders differed significantly from those who responded well to drug therapy.

Patients and Methods

The study group comprised 53 females with idiopathic detrusor instability; 48 of these patients completed oxybutynin treatment and 42 completed both oxybutynin and placebo. The mean age of those completing oxybutynin treatment was 46.2 years (SD 12.0, range 22–75) and mean parity was 2.2 (SD 1.6, range 0–6). The mean duration of symptoms was 8.2 years (SD 8.5, range 1–30 years). The mean number of voids/day was 11.6 (SD 6.9, range 7.5–24.5).

Urodynamic status

Medium-fill subtraction cystometry was performed using 500 ml of sterile saline at 37°C. The mean volume at first desire to void was 100.4 ml (SD 84). The mean maximum detrusor pressure during filling or provocation was 57.5 cm H_2O (SD 25) and the mean cystometric capacity was 282 ml (SD 166).

A brief explanation about the nature of detrusor instability was given at recruitment to the trial: no specific habit training or psychotherapy was employed. The response to placebo and oxybutynin therapy was measured by cystometry. All assessments were performed by the same observer (K.H.M.), who was unaware of which treatment had been administered.

Analysis of treatment response

In order to distinguish good responders from poor responders the percentage improvement was calculated for changes in volume at first desire to void and maximum detrusor pressure respectively; these figures were combined to give a percentage response for each patient. (Maximum cystometric capacity was excluded because oxybutynin was frequently associated with an improvement to the maximum possible of 500 ml; hence this parameter poorly differentiated the relative treatment response). Patients were grouped into $\leqslant 49\%$ response and $> 50\%$ response.

Psychoneurotic status

At the first visit, a review of stressful life events (Holmes and Rahe, 1967) and an enquiry into previous medical conditions were undertaken, including a history of nocturnal enuresis or childhood frequency/urgency of micturition and history of irritable bowel syndrome.

The Crown Crisp Experiential Index (CCEI) identifies neurotic traits such as free-floating anxiety, phobic anxiety, obsessionalism, somatic complaints, depression and hysteria. The published subscale values for normal urban females and for female psychoneurotic out-patients (Crown and Crisp, 1979) are shown in Table 1. Psychometric testing was performed at the end of the drug trial in order to avoid discussion about neurotic attributes during the study.

Results

Psychoneurotic status and treatment response

Six of the 53 subjects had suffered from persistent primary nocturnal enuresis beyond the age of 8 years. However, there was wide variation in the Crown Crisp scores and response rates (mean response 41%, range 0–125) for such patients (Table 2). Thirteen patients (25%) had undergone laparoscopy for abdominal pain, accompanied by bloating, constipation and a variety of gynaecological symptoms. No abnormality was found and after full assessment these patients had been assigned a diagnosis of irritable bowel syndrome by the referring clinician. Crown Crisp scores for these patients also varied greatly; the percent response tended to be low (mean 38%, range 0–85).

When asked about stressful life events around the onset of urinary symptoms, 25 patients recalled a major bereavement, marital stress or stressful childbirth. Eight patients felt that symptoms began shortly after hysterectomy. Twenty-eight patients could not recall a precipitating factor; of these, 6 had persistent nocturnal enuresis and 2 were under long-term psychiatric treatment. No obvious trend in Crown Crisp Score or treatment response was seen in any of these patients.

Treatment response in relation to psychometric score

Of the 48 patients who received oxybutynin, 2 could not read or write; 40 questionnaires (87%) were returned. The duration of incontinence symptoms did not correlate with the mean total Crown Crisp score ($r = -0.273$) or with any of the subscale scores.

The mean Crown Crisp score of patients who

Table 1 Combined Percentage Improvement in First Desire to Void and Maximum Detrusor Pressure In Relation to Crown Crisp Score

	After oxybutynin treatment (N=40)						
	Anx	*Pho*	*Obs*	*Som*	*Dep*	*Hys*	*Total*
Normal females	5.4	4.7	7.4	5.7	4.4	2.9	33.5
50–450% Improvement (N=20)	6.4	5.3	6.2	6.2	4.0	2.6	30.7
<49% Improvement (N=20)	8.8	6.8	8.1	8.9	6.6	4.5	43.7
Psychoneurotic out-patients	11.0	6.8	8.2	8.9	7.6	5.2	47.7

Anx: Free-floating anxiety. Pho: Phobic anxiety. Obs: Obsessionalism. Som: Somatic complaints. Dep: Depression. Hys: Hysteria.

Table 2 Medical Conditions/Precipitating Factors in Relation to Crown Crisp Score and Response Rate

Medical condition/precipitating factor	*No. of patients (N=53) (%)*	*No who completed oxybutynin and CCEI (N=40)*	*Mean CCEI score (SD)*	*Mean % response to drug (SD)*
Persistent nocturnal enuresis	6 (11)	6	45.6 (15.6)	41.3 (44)
Childhood frequency/urgency	5 (9)	4	26 7 (10.5)	128 (170)
Irritable bowel syndrome	14 (25)	9	37.3 (15.5)	38 (31)
Chronic psychiatric care	7 (13)	5	47 0 (14 4)	81 (89)
Chronic insomnia	4 (7)	3	57.0 (7.0)	56 (61)
After bereavement	5 (9)	5	46.0 (15 5)	79 (92)
Marital upset	7 (13)	4	41.8 (25.0)	50 (47)
After childbirth	5 (9)	3	21 3 (4.5)	114 (147)
After hysterectomy	8 (15)	7	48.6 (14.2)	112 (168)
No precipitating factor	28 (53)	20	33.9 (34.0)	69 (89)

responded well to oxybutynin (30.7, SD 13.6) was similar to that of normal urban females (33.5, SD 12.5). The mean Crown Crisp score of patients who responded poorly to drug therapy (43.7, SD 15.4) was significantly higher than for the good responders ($P<0.01$) and approached the score for female psychoneurotic out-patients (47.7).

Comparison of results for 3 subscales (phobic anxiety, obsessionalism, somatic complaints) showed a marked similarity between the poor responders and psychoneurotic out-patients (Table 1). However, within the group of poor responders, 2 subgroups were identified. Two-thirds of patients had grossly abnormal scores (mean 52.8, range 39–70, SD 10.3, N=13), whilst one-third had normal scores (mean 26.8, range 19–34, SD 5.5, N=7).

Placebo response versus psychometric score

For patients who completed both placebo therapy and psychometric testing (36/42=86%) the relationship between response to placebo and mean Crown Crisp score is shown in Table 3. Seven patients showed a deterioration in their condition after placebo treatment. No association between placebo response and Crown Crisp score was seen.

Discussion

In 1949, Straub *et al.* showed that emotional

Table 3 Combined Percentage Improvement in First Desire to Void and Maximum Detrusor Pressure In Relation to Crown Crisp Score

	After placebo treatment (N=36)						
	Anx	*Pho*	*Obs*	*Som*	*Dep*	*Hys*	*Total*
>50% Improvement (N=12)	8.6	6.8	8.2	7.6	5.8	4.9	42.5
<49% Improvement (N=17)	7.2	4.8	7.2	7.5	4.7	2.8	34.2
0–100% Decline (7)	7 6	6.7	6.0	7.7	6.3	3 7	38.0

Abbreviations as in Table 1.

disturbance during cystometry provoked detrusor contractions in 7 of 18 patients. Macauley *et al.* (1987) repeated this study using modern subtraction cystometry: only 1 of 6 patients showed detrusor contractions that were not simultaneous with the stressful topic.

Jeffcoate and Francis (1966) found that 61% of 246 patients with urge incontinence appeared obsessional or depressed; 15% also suffered from "spastic colon". Of those without psychological problems, 54% had noted frequency of micturition since childhood. Frewen (1978) postulated that urge incontinence developed as a result of psychic trauma but provided few details to substantiate this view. Neither study used psychometric tests.

Crisp and Sutherst (1983) found that 15 patients with detrusor instability were more neurotic according to the Eysenck Personality Questionnaire than 42 patients with genuine stress incontinence (GSI), which agreed with a study of depression and life events by Pierson *et al.* (1985). In contrast, Morrison *et al.* (1986) found no significant difference in the Eysenck Personality Inventory (EPI) score between 115 women with detrusor instability and 50 other incontinent patients, but 61 subjects were excluded because of high scores on the Lie Subscale of the test.

Macauley *et al.* (1987) showed that 32 women with detrusor instability had higher anxiety and hysteria scores on the Crown Crisp Index than 113 patients with sensory urgency or GSI. Test scores did not change significantly after propantheline treatment for detrusor instability (Macauley, 1988).

Previous attempts to correlate psychoneurotic status with the outcome of treatment have yielded conflicting results. Hafner *et al.* (1977) found that 50% of the "most neurotic" patients benefited from psychotherapy but only 11% of the "least neurotic" improved. The authors felt that the "least neurotic" subjects (on EPI score) actually denied their neuroticism, but scores from the Lie Scale were not documented to support this theory. Ferrie *et al.* (1984) found that poor responders did tend to have more neurotic EPI scores. Millard and Oldenburg (1983) felt that only 1 of 4 psychometric tests (Composite Psychosocial Index) helped to predict treatment response.

In keeping with previous authors, we found a high prevalence of childhood frequency of micturition or prolonged bedwetting (20%) and irritable bowel syndrome (25%) in women with detrusor instability. Although these are often thought to be psychosomatic conditions, we found no consistent trend in the psychometric scores of such patients, suggesting that this symptom cluster may not reflect a common disorder of the psyche but perhaps some neurophysiology abnormality. The poor treatment response of those with bedwetting and irritable bowel syndrome may also support such a concept.

The Crown Crisp scores of patients who recalled a traumatic life event at the onset of symptoms were extremely variable (Table 2); thus there is little evidence in favour of psychic trauma as a cause of detrusor instability.

Patients who responded well to simple anticholinergic therapy had a mean Crown Crisp score which was similar to that of the general population. This suggests that there is a subgroup of detrusor instability patients who are not psychoneurotic. Whilst the placebo response in psychosomatic conditions is often believed to be high, we found no relationship between good placebo response and abnormal psychoneurotic score. This may cast further doubt upon the idea that idiopathic detrusor instability is largely a psychosomatic disorder.

The mean Crown Crisp score for the group of poor responders was abnormally high and was similar to published scores for psychoneurotic outpatients. Although two-thirds of our poor responders had grossly abnormal scores, the fact that one-third had normal scores suggests several possibilities. The psychometric test we used may be inaccurate or patients may "fake" their responses (despite extensive validation studies of this test (Alderman *et al.*, 1983)). In addition, cystometry may not be the best indicator of treatment success, or poor treatment response is not necessarily associated with neuroticism.

The last suggestion would be in keeping with a hypothesis that idiopathic detrusor instability may result from a physical abnormality. In this regard, the relationship between persistent enuresis and subsequent detrusor instability (Fergusson *et al.*, 1986) and the connection between irritable bowel syndrome and bladder dysfunction (Whorwell *et al.*, 1986) merit further study. Similarly vasoactive intestinal polypeptide (Gu *et al.*, 1983), serotonin (Klarskov and Hørby-Petersen, 1986) and other neuropeptides which may play a part in the aetiology of detrusor instability require more investigation.

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The Authors

Kate H. Moore, MRCOG, MRACOG, formerly Registrar, Department of Gynaecology, Princess Royal Hospital, Hull. Now Lecturer, Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, University of Liverpool.

J. R. Sutherst, MD, FRCOG, Consultant Gynaecologist, Arrowe Park Hospital; Honorary Director, Professorial Urodynamic Unit, University of Liverpool.

Requests for reprints to: Kate H. Moore, University Department of Obstetrics and Gynaecology, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

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Double-blind, Placebo-controlled, Cross-over Study of Flavoxate in the Treatment of Idiopathic Detrusor Instability

C. R. CHAPPLE, H. PARKHOUSE, C. GARDENER and E. J. G. MILROY

Department of Urology, Middlesex Hospital, London

Summary—Detrusor instability occurs in approximately 10% of the adult population, producing troublesome symptoms. The pharmacotherapy currently available is usually only partially effective and cannot be adequately evaluated except under "blind" conditions because of the significant component attributable to placebo effects. The results of the present study revealed no advantage resulting from treatment with flavoxate, as assessed both subjectively and objectively. We suggest that this therapy does not appear to be beneficial in the medical management of detrusor instability.

Flavoxate hydrochloride (N-piperidinoethyl 3-methyl flavone-8-carboxylate hydrochloride) is a tertiary amine compound which has been demonstrated *in vitro* to have potent smooth muscle relaxant properties (Grazianai *et al.*, 1983). Previous clinical studies have suggested a significant improvement in detrusor instability during treatment with this drug (Stanton, 1973; Ruffman and Sartani, 1987) but this has not been confirmed by all workers in the field (Briggs *et al.*, 1980). The pre-existing data have been derived from studies which were either "open" or which contrasted flavoxate with other pharmacological therapy no longer considered effective in the treatment of detrusor instability (Ruffman and Sartani, 1987). The aim of this study was to carry out the first controlled cross-over trial contrasting the efficacy of flavoxate 200 mg *tds* with placebo in the treatment of detrusor instability.

Patients and Methods

A total of 41 patients with idiopathic detrusor instability confirmed at videocystometry were included in the study; all gave full informed consent. Strict exclusion criteria were enforced and case selection was reviewed by the trial monitor at the end of the study. These criteria included coexisting bladder outflow obstruction, associated overt neurological disease and coexisting medical conditions that were thought to have a potential effect on the bladder.

Ten patients failed to complete the study; 8 of these were completely excluded for violation of the protocol; 2 were included in the raw mean data as they were not protocol violators, but not in the subsequent formal Hills-Armitage analysis (1 patient failed to complete the first treatment period and the other withdrew with adverse effects after 48 h) (Table 1). A further 7 patients were excluded

Table 1 Adverse Side Effects

Patient no	*Visit Week*	*Drug*	*Adverse effect*	*Severity*	*Relation to test drug*
4	3	P	Bowel frequency	Mild	Unknown
5*	6	U	Ankle swelling	Mild	Unknown
8*	6	P	Dry mouth	Mild	Probably related
12*	6	U	Weight gain	Mild	Unknown
16	3	P	Hot flush	Mild	Probably related
26†	2 days	U	Nausea General lethargy Malaise	Severe	Unknown

* Protocol violators—not included in efficacy analysis
† Patient withdrew because of adverse effects.
U = Flavoxate P = Placebo

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Table 2 Active Co-Existing Disease/Concomitant Medication

Patient no.	*Disease*	*Medication*
2	Previous TURP	None
3*	SLE	Hydroxychloroquine
4	Previous TURP	None
5*	Insomnia	Serenid
8*	Previous TURP	None
	Angina	Aspirin Verapamil Isosorbide GTN Persantin
11*	Hypertension	Aldomet
12*	Prolapsed intervertebral disc	Diazepam
13*	Depression	Lorazepam Prothiadine
27	Carcinoma breast	None
28	Peptic ulcer	Ranitidine
30*	Diabetes	Insulin
32	Hypothyroidism	
39	Fibrosing alveolitis	Prednisolone
40	Hypothyroidism	Thyroxine

* Patient withdrawn by trial monitor prior to statistical analysis of data because of the medical circumstances depicted here.
TURP = Transurethral resection of prostate.
SLE = Systemic lupus erythematosus

during analysis of efficacy by the trial monitor because of coexisting medical conditions or pharmacological treatment (Table 2), leaving 25 patients suitable for efficacy analysis (Table 3). There were 13 males and 12 females (mean age 51 ± 3 years).

Throughout the 6-week study period the patients recorded their 24-h voiding frequency on diary cards. After an initial period of 1 week on no medication, they were randomised to receive either flavoxate hydrochloride 200 mg or placebo 3 times a day. After 2 weeks of treatment a further videocystometrogram was carried out and during the fourth week of the study no treatment was given. The patients were then crossed over to alternative therapy of placebo or flavoxate respectively for a further 2 weeks, followed by a final videocystometrogram (Fig.).

Sixteen patients received flavoxate followed by placebo and 17 received placebo followed by flavoxate. Thus only 1 patient completed the first but not the second treatment period. An analysis including this 1 patient in a 2-sample comparison of efficacy based on the first period only showed no significant findings and is therefore not considered further here. Patient preference for each week of

Table 3 Demography of Patients Included in Efficacy Analyses

	Flavoxate/ placebo (n=11) Mean (SD)	*Placebo/ flavoxate (n=14) Mean (SD)*	*Total (n=25) Mean (SD)*	*P*
Age (years)	46.7 (18.5)	54.4 (11.7)	1.0 (15.2)	0.19*
Frequency (average times per day)	12.5 (7.1)	11.6 (5.4)	12.0 (6.1)	0.76*
Nocturia (average times per day)	4.5 (3.5)	2.4 (1.7)	3.3 (2.8)	0.11*
Sex				
Male	6	7	13	1.00†
Female	5	7	12	
Urinary incontinence				
Usually	2	8	10	0.024‡
Sometimes	4	0	4	
Rarely	5	6	11	
Stress incontinence				
Usually	0	0	0	1.00†
Sometimes	2	2	4	
Rarely	9	12	21	
Urgency				
Usually	8	11	19	1.00†
Sometimes	3	3	6	
Rarely	0	0	0	
No significant differences between the groups				

* Mann Whitney test for difference between groups.
† Fisher's exact test (2-tailed)
‡ χ^2 test.

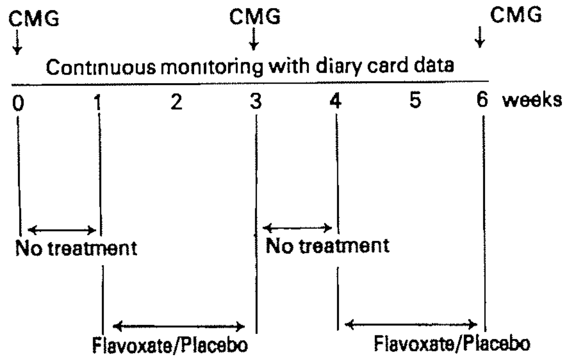

Fig. Treatment protocol

treatment was documented. During the study the following data were recorded:

(1) Daily voiding frequency
Nocturia
Daytime frequency
DIARY CARDS

(2) Patients' preference for each week's "drug treatment".

(3) Urodynamic parameters: free flow rate, maximum filling detrusor pressure, detrusor pressure at the end of bladder filling, maximum voiding detrusor pressure, bladder capacity, bladder volume at onset of detrusor instability, bladder volume at which incontinence occurred, bladder residual volume, videocystometry.

Statistical Analysis

The pre-treatment characteristics of the 2 groups were compared using the Mann-Whitney test, Fisher's exact test and Pearson's χ^2 test as appropriate. Tests for carryover, order and treatment effects were performed using the standard Hills-Armitage technique with the Mann-Whitney rank sum test (Hills and Armitage, 1979). In addition, a "raw" analysis of changes from baseline within each group and differences between the groups, overall and at each visit, was carried out using the Wilcoxon signed rank and Mann-Whitney rank sum tests respectively.

Results

Adverse Effects

Of the 6 patients who reported adverse effects (Table 1), 3 were on placebo and 3 on flavoxate. Three of these patients (2 of whom were on active treatment) were also protocol violators and hence were not included in the final efficacy analysis.

Analysis of Cystometric Data

Differences between the flavoxate and placebo groups were analysed using the Hills-Armitage method, which did not demonstrate a significant carryover effect; the probability values were obtained using the Mann-Whitney rank sum test (Table 4). In addition, changes from baseline values within treatment were analysed using the Wilcoxon matched pairs test. None of these analyses suggested any statistically significant clinical difference when contrasting both agents. This is demonstrated by a perusal of the data in the format of mean differences between flavoxate and placebo (Table 4).

Analysis of Diary Card Data

A review of diary card data (Table 5) revealed that

Table 4 Analysis of Cystometric Data (Cystometric data expressed as the difference between treatments assuming no carryover).

	Mean difference (U-P)	*Standard error*	*P**	*95% CI*	
				Lower	*Upper*
Maximum pressure rise (cm H_2O)	−0.68	3.77	1.00	−8.30	6.94
End filling pressure (cm H_2O)	−5.32	4.28	0.27	−13.97	3.33
Volume at commencement of pressure rise (ml)	−32.53	21.66	0.55	−76.30	11.24
Volume at which incontinence occurred (ml)	25.25	65.40	1.00	−122.68	173.18
Final tolerated filling volume (ml)	−10.79	15.85	0.57	−42.82	21.24
End residual volume (ml)	−2.32	6.82	0.62	−16.10	11.46
Free flow rate (ml/s)	1.80	1.93	0.38	−2.10	5.70
Maximum voiding pressure (cm H_2O)	6.99	7.29	0.17	−7.74	21.72

No significant differences between flavoxate and placebo
*Mann-Whitney rank sum test (from Hills-Armitage analysis)
U = Flavoxate
P = Placebo.

Table 5 Analysis of Dairy Card Data (Mean no. of voids/24 h: difference between changes from baseline (assuming no carryover)

	No.	*Mean*	*SD*	*P**
Flavoxate—placebo after 1 week	24	−0.167	3.03	0.95
Flavoxate—placebo after 2 weeks	24	−0.292	5.09	0.95

* Wilcoxon signed rank test for paired differences.

neither flavoxate nor placebo produced significant changes in voiding patterns. On subjective assessment of the treatment, patients could not reliably differentiate between active treatment and placebo.

Discussion

This study has failed to demonstrate any significant difference between flavoxate 200 mg *tds* and matched placebo in the treatment of detrusor instability, using both objective and subjective criteria. It has been suggested that flavoxate may have increased efficacy in Asiatic races using a similar dosage (Fang-lui *et al.*, 1987) and on this basis it has been suggested that an increased dose range may be more effective. Although this appears an attractive hypothesis, double-blind controlled studies need to be carried out. At present it must be concluded that there is little evidence to support the continued use of this drug at the currently recommended dose range in the pharmacological therapy of detrusor instability.

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The Authors

C R Chapple, FRCS, Senior Urological Registrar, Middlesex Hospital.

E. J. G Milroy, FRCS, Consultant Urologist, Middlesex Hospital

H. Parkhouse, FRCS, Senior Urological Registrar, St Bartholomew's Hospital, London

C Gardener, BSc, DipBiom, Senior Statistician, Syntex Pharmaceuticals Ltd, Maidenhead.

Requests for reprints to: C. R. Chapple, Department of Urology, Middlesex Hospital, Mortimer Street, London W1N 8AA.

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The Perineal Artificial Sphincter for Acquired Incontinence—a Cut and Dried Solution?

D. J. WARWICK and P. ABRAMS

Department of Urology, Southmead Hospital, Bristol

Summary—Sixteen males with stress incontinence due to sphincter damage were investigated with videourodynamic studies after implantation of a perineal artificial urinary sphincter. Twelve patients were rendered dry; 4 remained incontinent, all of whom were shown by cystometry to have incontinence from detrusor instability. Of these, 2 also had stress incontinence proven by videourography.

Detrusor instability was present in 9 patients before implantation; the instability worsened considerably in 2 patients and new instability was shown in another 2 patients.

The limitations of the artificial urinary sphincter and the implications of detrusor instability in patients with an artificial sphincter are discussed.

The artificial urinary sphincter is an extremely successful device for the treatment of acquired stress incontinence.

Early methods of treating sphincteric stress incontinence with constant pressure implants such as the Kauffman prosthesis have been superseded over the past 15 years by variable pressure inflatable devices, the latest modification being the AMS 800 (Whitaker, 1985). It is accepted that implantation of the artificial urinary sphincter (AUS) is a successful method of treating stress incontinence in appropriate patients (Goldwasser *et al.*, 1987; Nurse and Mundy, 1988). The sphincter may be implanted in the perineum or around the bladder neck (Furlow and Barrett, 1985).

It is generally agreed that urodynamic evaluation should be carried out before implantation of the AUS, particularly to assess the relative contribution of detrusor instability and sphincter weakness to the patient's incontinence. Recent work has suggested that the AUS may alter detrusor behaviour in patients with congenital neuropathic incontinence (Light and Pietro, 1986; Murray *et al.*, 1988).

We investigated the clinical and urodynamic effect of the implantation of an AUS on patients with acquired incontinence in order to assess the efficiency of the device and to determine whether bladder muscle behaviour was altered by surgery.

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Patients and Methods

Between October 1984 and February 1989, 19 perineal artificial sphincters were implanted. The aetiology of the patients' incontinence is shown in Table 1. In each patient an AUS 800 sphincter was used, with a 51–60 cm H_2O balloon and a 4.5 cm occlusive cuff. The AUS was implanted between 9 months and 16 years after the sphincter damage. Two patients died from unrelated causes and were thus not available for follow-up. One patient had incontinence following a head injury and frontal lobe damage as a child. Because of this complex aetiology to his incontinence he was not included in this report. Thus 16 patients were studied.

Pre-operative and post-operative videourodyn-

Table 1 Aetiology of Incontinence

		Included in study
Pelvic trauma	3	3
Post-prostatectomy Retropubic	7	6
Transurethral	7	6
Congenital urethral anomaly	1	1
Skull fracture	1	
Total	19	16

amic studies were performed on all patients. All of the post-operative studies were carried out by the same investigator.

An initial flow rate was determined. The urethral pressure profile was measured with an 8F Porges catheter using the Brown and Wickham (1969) technique. The profile was recorded with the sphincter cuff inflated and then deflated. The pump was squeezed 5 times to ensure total deflation and this was confirmed on the trace. A cystometrogram was performed with the patient standing. Filling was at 30 ml/min with Urografin contrast at room temperature through an 8F catheter. Intravesical pressure was measured with an epidural catheter placed in the bladder. The intra-abdominal pressure was measured with an 8F catheter passed into the rectum. Data were recorded on a Dantec Type 21, 6 channel recorder. Filling and voiding were screened with a Seimens image intensifier. The catheter was removed before the voiding stage.

Urodynamic detrusor instability was defined as a bladder which contracted during filling whilst the patient was trying to inhibit micturition.

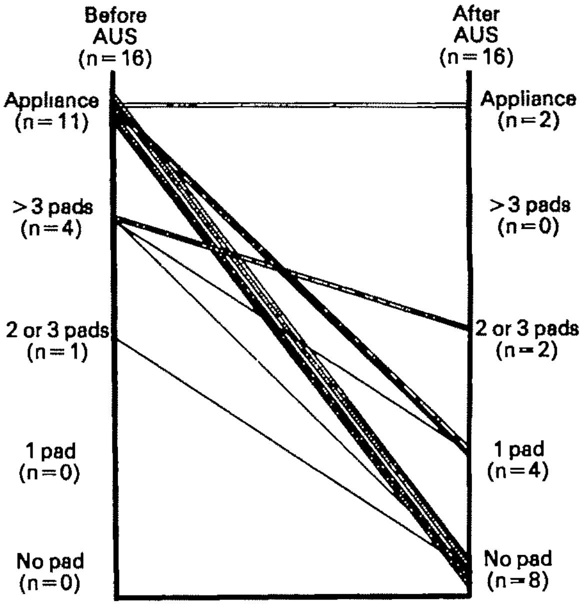


Fig. 1 Improvement in continence after implantation of the AUS.

Results

Continence

Of the 16 patients, 8 had total relief of their incontinence (Fig. 1). The others still required protection. Four needed only 1 pad daily—this was not considered to be significant either by the patient or by the investigator. Two patients needed 2 or 3 pads daily and claimed that their incontinence was greatly improved. Two patients needed a convene; both reported that their previous continuous dribble had been converted to intermittent incontinence. No patient reported a worsening of incontinence after surgery.

The patients were asked whether the AUS had improved their quality of life. Twelve reported a great improvement. Of the 4 reporting little or no improvement, 2 still needed a convene. Of the other 2, 1 was a stoic who had refused to let his quality of life be compromised when he was incontinent before AUS implantation; 1 had his lifestyle severely restricted by other medical conditions.

Only 2 patients continued to have sexual intercourse. Neither of them deflated the sphincter and they passed little or no semen.

Flow rates

Pre-implantation flow rates were invalid because of the low bladder volumes in the incontinent patients. Post-implantation flow rates ranged from 5 to 40 ml/s. The patient with a flow rate of only 5 ml/s had urethral scarring following the implantation of iodine seeds for prostatic cancer. The next lowest rate was 10 ml/s in a patient whose urethra had been traumatically disrupted. Three of the post-prostatectomy patients had flow rates <15 ml/s and 5 had flow rates of >25 ml/s. The flow rates were not determined by residual cuff pressure, since urethral pressure profile measurement proved that the AUS was mechanically functioning and not producing outflow obstruction after deflation (*vide infra*).

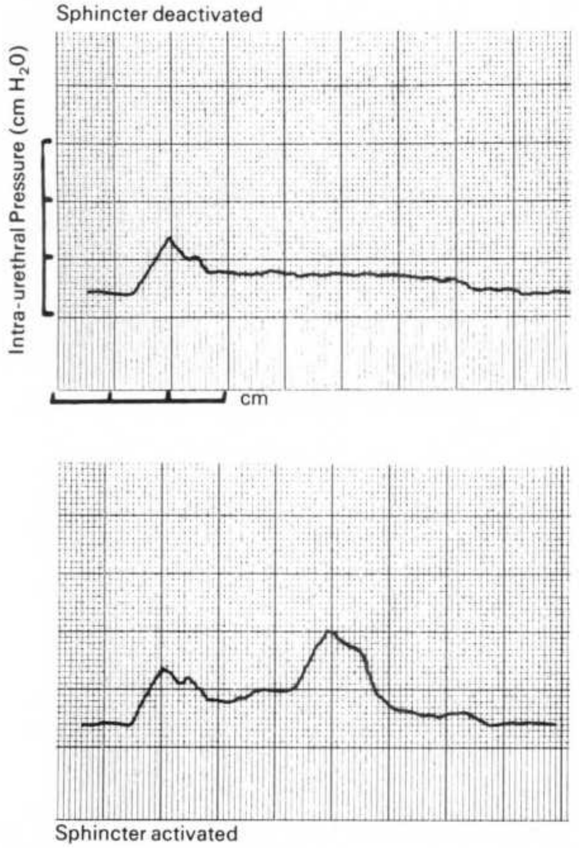
Urethral pressure profile

A typical urethral pressure profile with the sphincter inflated and deflated is depicted in Figure 2. Fourteen patients had similar profiles, with no detectable pressure trace at the site of the AUS after deflation. In 2 patients the profile was different, due to a probable stricture in 1 and to possible mucosal folding or residual cuff pressure in the other.

There was no correlation between the urethral closure pressure at the level of the AUS and symptomatic or videourodynamic evidence of incontinence.

Videocystometry

The bladder and prostatic cavity typically fill with contrast, with a column of urine held competently


Sphincter deactivated

Sphincter activated

Fig. 2 Urethral pressure profile.

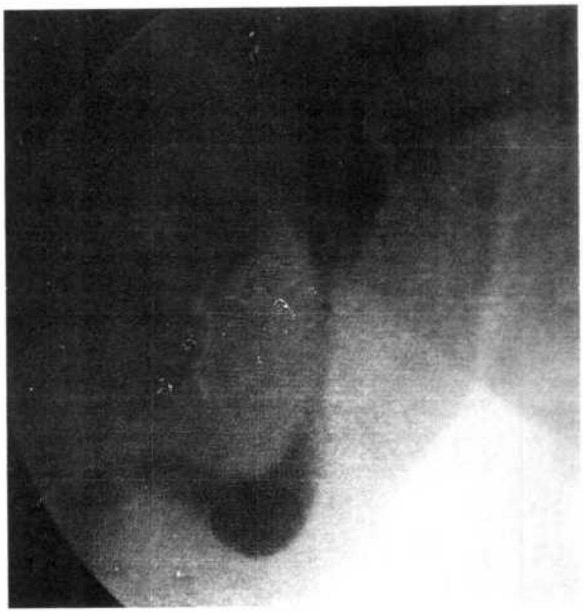


Fig. 3 Stress incontinence.

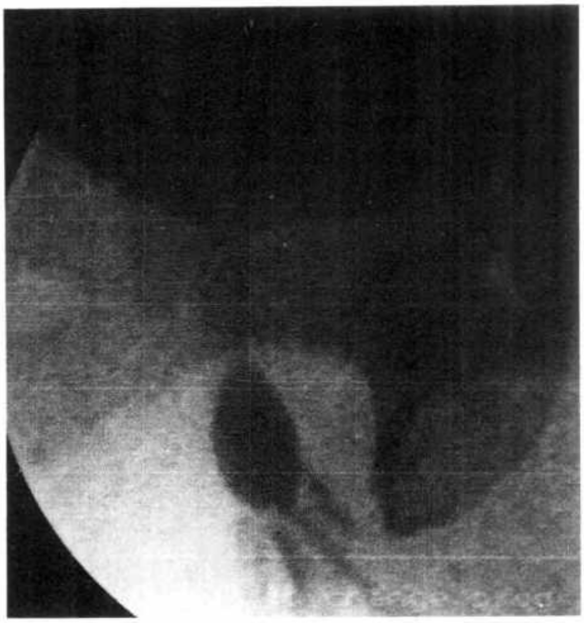


Fig. 4 Unstable wave; column of urine held by artificial sphincter with proximal dilatation.

by the AUS and some dilatation proximal to it. Stress incontinence was demonstrated in 3 patients (Fig. 3).

Detrusor instablility (DI) was present in 9 of the 16 patients before implantation of the AUS. In none of the patients did this disappear. DI was present in 11 patients post-operatively. New DI appeared after implantation in 2 patients, of whom 1 needed 3 pads daily and the other was dry. The severity of DI (higher amplitude/more frequent waves) was greater in 2 patients; 1 was dry and the other needed only 1 pad daily. DI was reduced in 1 patient. Of the 11 patients with DI, 5 needed no pads and 6 needed protection: 2 needed only 1 pad, 2 needed a convene and 2 needed 2 or 3 pads daily (Table 2). Videourography showed contrast to be held competently at the AUS with some proximal dilatation during an unstable wave in the 5 dry patients (Fig. 4); in the 6 wet patients, contrast was shown to leak during an unstable wave.

Of the 2 patients needing a convene, 1 had stress incontinence and DI and 1 had only DI. The latter patient did not respond to medical therapy and refused augmentation cystoplasty. Of those needing 2 or 3 pads, 1 had stress incontinence and DI; the other had only DI (Table 2).

Table 2 Causes of Persisting Incontinence after Implantation of the AUS

Patient no.	*Protection*	*DI*	*Stress*
1	Convene	+	+
2	Convene	+	–
3	3 pads	+	+
4	2 pads	+	–
5	1 pad	+	+
6	1 pad	+	–
7	1 pad	–	–
8	1 pad	–	–
9–16	0 pad	5	0

Discussion

The perineal AUS is effective and produces marked improvement in most patients. Persisting incontinence may be due to inadequacy of the cuff pressure to resist rises in intra-abdominal pressure: this can be regarded as inadequate prosthetic surgery.

Persisting stress incontinence is more common with perineal than with bladder neck artificial sphincters (Sidi *et al.*, 1984), probably because there is no transmission of intra-abdominal pressure to the cuff in the perineal position. It is technically difficult to avoid stress incontinence because of the risk of cuff erosion if a high pressure system is implanted. Cuff erosion is thought to be a greater problem in the perineal location because of the thinner, less vascular and more mobile tissue (Diokno *et al.*, 1984), although no case of erosion was seen in this study.

If persisting incontinence is proven to be due to stress incontinence, it is possible to increase the pressure of the regulating balloon, but this would involve a second operation and would increase the risk of cuff erosion. Thus one might prefer to use a low pressure system, particularly with a perineal AUS, and accept that mild stress incontinence is preferable to the risk of cuff erosion. The patients should be counselled accordingly.

After insertion of an AUS, incontinence is more likely to be due to DI than to stress incontinence. This may be either pre-existing or new detrusor instability. This incontinence should not be remedied by attention to the cuff, since the cuff is designed to overcome only stress incontinence. Incontinence caused by detrusor instability warrants attention to the bladder itself, with trials of anticholinergic therapy and, in intractable cases, consideration of augmentation cystoplasty.

The development of detrusor instability in the congenital neuropathic bladder after implantation of an artifical urinary sphincter is recognised (Light and Pietro, 1986; Murray *et al.*, 1988); upper tract deterioration can be expected in a small proportion of these cases (Brantley Scott *et al.*, 1986; Roth *et al.*, 1986). Thus a regular review of the upper tracts is recommended for patients with neuropathic bladders and an artificial sphincter.

All patients in this study had normally innervated bladders with damaged sphincters which had been treated by implantation of the artificial sphincter. Four patients had either new or worsened detrusor instability after surgery. One of these had marked bladder trabeculation with reflux of urine into one ureter during a high pressure unstable wave. The trabeculation and reflux had not been apparent with pre-operative videourodynamics. This patient was continent, suggesting that the high bladder pressures during an unstable wave would not be vented through the urethra because of the presence of the artificial sphincter. This reinforces the conclusion that leakage due to detrusor instability should not be regarded as a failure of the artificial sphincter.

The cause of the altered detrusor stability is unclear. It has been suggested that in the congenital neuropathic bladder, DI becomes apparent after AUS implantation because the bladder can then fill to a greater volume without leakage, thus exposing DI which was not demonstrable in the bladder kept at low volume by incontinence (Murray *et al.*, 1988). However, the 4 patients in the present study with new or exacerbated DI were all filled during pre-AUS urodynamics with the aid of a penile clamp; in each case a volume was achieved greater than that at which instability was demonstrated in post-AUS urodynamics. This suggests that the new or worsened DI is a genuine phenomenon.

It was concluded that the artificial sphincter is successful and that detrusor instability is the usual cause of persistent incontinence. Since DI may also lead to long-term upper tract problems in some patients, close surveillance is advisable. This potential problem in the normally innervated bladder needs further evaluation.

Acknowledgements

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The Authors

D. J Warwick, BM, Senior House Officer.
P. Abrams, MD, FRCS, Consultant Urologist

Requests for reprints to: P. Abrams, Department of Urology, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB.

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Foley Catheter Balloon Puncture and the Risk of Free Fragment Formation

J. M. CHRISP and J. N. NACEY

Department of Surgery, Wellington School of Medicine, Wellington, New Zealand

Summary—The incidence of free fragment formation following balloon puncture or spontaneous bursting was examined in 294 Foley catheters immersed for 48 h in urine. The catheters were divided into 3 groups: 100 were inflated to the manufacturer's recommended volume, 100 to twice the volume and 94 to 3 times the recommended volume. The catheter balloons were punctured by pricking with a hypodermic needle.

The overall incidence of free fragment formation was 27.3%. For both types of catheter examined, increasing balloon volume was not associated with an increased risk of free fragment formation following puncture. However, increasing volume was associated with increased free fragment formation when the balloon burst spontaneously.

In view of the high risk of free fragment formation, cystoscopy should be performed in all cases of spontaneous catheter balloon rupture or after percutaneous balloon puncture.

Failure of a self-retaining balloon catheter to deflate is a common problem which may cause distress to the patient and frustration for the clinician. A number of techniques for deflating or bursting balloons have been tried. These include the instillation of chloroform or acetone via the inflation channel (Chin *et al.*, 1984), passing a fine wire along the inflation channel to unblock it or burst the balloon (Sood and Sahota, 1972; Lutin and Mullins, 1982; Hessl, 1983; Browning *et al.*, 1984; Chin *et al.*, 1984) and percutaneous puncture, either unassisted or with the assistance of X-ray or ultrasound guidance (Moisey and Williams, 1980; Kleeman, 1983; Lau, 1983; Chin *et al.*, 1984; Houghton and Foster, 1984; Moskovich, 1984; Moffat *et al.*, 1985).

The problems encountered with the use of solvents (Sood and Sahota, 1972; Moisey and Williams, 1980; Kleeman, 1983) or passage of a fine wire (Kleeman, 1983; Arkell, 1984; Houghton and Foster, 1984; Moskovich, 1984; Mukhtar and Orr, 1984) have meant that balloon puncture is the procedure of choice. In many instances the balloons are inflated beyond the manufacturer's recommended volume to offer a bigger target for the needle. However, puncture may result in the formation of balloon fragments which may remain in the bladder following removal of the catheter (Lutin and Mullins, 1982; Kleeman, 1983; Moskovich, 1984). These fragments may then become encrusted with clacium deposits, leading to irritative symptoms and chronic infection (Hukins *et al.*, 1983).

The aim of this study was to assess the incidence of free fragment formation following balloon rupture and to record any difference according to overdistension of the balloon.

Materials and Methods

A total of 300 new, unused Foley catheters of 2 different types were tested. The first was a teflon-coated latex catheter with a horizontal ribbed balloon of 30 ml recommended volume. There were 150 catheters from 10 different batches in this group. The second type was an all-silicone catheter with a horizontal ribbed balloon of 30 ml recommended volume. There were 150 catheters from 8 different batches in this group.

Each group of catheters was divided into 3

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subgroups each of 50 catheters for testing. The first subgroup was inflated to the manufacturer's recommended balloon volume (30 ml). The second group was inflated to twice the recommended volume and the third to three times the recommended volume. All balloons were inflated with distilled water. Care was taken to include equal numbers of catheters from different batches in each group.

Following inflation of the balloon, the catheters were immersed in fresh urine collected from healthy adult volunteers. The catheters were immersed for 48 h with the urine temperature maintained at 37° C. Those catheters with balloons intact at the end of the 48 h had the balloon punctured by pricking at the mid-point with a 22 gauge needle. The number of catheters producing free fragments following puncture was recorded. The balloons of some catheters burst either during inflation or spontaneously while immersed in the urine bath. The number of these catheters and the number producing free balloon fragments were also recorded.

Fisher's exact probability test was used to establish the significance of the differences observed.

Results

The results are shown in the Table. Of the 150 teflon-coated catheters, 44 (29.3%) produced a free fragment either during spontaneous rupture or following balloon puncture. The rate of free fragment formation following puncture did not increase significantly with increasing balloon volume. However, as the volume increased the number of balloons bursting spontaneously did increase and of these the number producing free fragments was greater with the higher balloon volumes ($P=0.0001$). Six teflon-coated catheters burst during inflation to 90 ml but these did not produce free fragments.

Thirty-eight of the all-silicone catheters produced free fragments (25.3%). As with the teflon-coated catheters, the rate of free fragment formation following puncture did not increase with increasing balloon volume. As the volume increased the silicone catheters also showed a significantly higher rate of spontaneous bursting and with this a higher rate of free fragment formation ($P=0.0001$). None of the balloons of the all-silicone catheters burst during inflation.

Multiple fragment formation was not observed with either type of catheter. In each case of free fragment formation only 1 free fragment was produced per balloon. The fragment sizes ranged from 4 mm^2 to 370 mm^2 (mean 250 mm^2).

Discussion

Percutaneous puncture, using either X-ray or ultrasound guidance, is the safest and most fre-

Table Free Fragment Production from Teflon-coated Latex Catheters and All-silicone Catheters According to Balloon Inflation Volume

Inflation volume (ml)		*Teflon-coated catheter 30 ml horizontal ribbed balloon*		*All-silicone catheter 30 ml horizontal ribbed balloon*	
		Catheters (n)	*Free fragments (n)*	*Catheters (n)*	*Free fragments (n)*
30	Burst during inflation	0	0	0	0
	Spontaneous bursting	2	0	0	0
	Puncture	48	4	50	3
	Total	50	4	50	3
60	Burst during inflation	0	0	0	0
	Spontaneous bursting	7	3	6	4
	Puncture	43	7	44	10
	Total	50	10	50	14
90	Burst during inflation	6	0	0	0
	Spontaneous bursting	22	22	10	10
	Puncture	22	8	40	11
	Total	50	30	50	21

quently used method of bursting catheter balloons which resist normal deflation. The catheter balloons are usually over-inflated in the belief that this will provide a larger target for the probing needle. Puncturing the balloons produces fragments of rubber which may be retained in the bladder. The incidence of fragment formation has been previously estimated to be as low as 3.6% (Moskovich, 1984). Our study has shown a much higher incidence (27.3%), with similar rates for the teflon-coated (29.3%) and silicone catheters (25.3%).

Of interest is that increasing balloon volume *per se* does not lead to an increase in fragment formation, but volume is important in those catheters where the balloon bursts spontaneously. This may be related to an inherent weakness in the balloon wall. The catheters which we studied have horizontal ribbing of the balloons, which causes greater balloon symmetry. We had thought that the ribbing may strengthen and therefore limit the tearing of the balloons, but close examination showed that the single balloon fragments tore across the ribs and it must be assumed that horizontal ribbing offers little protection against fragment formation. Some catheters are manufactured with vertical ribbed balloons, but any association between vertical ribbing and fragment formation has not been assessed in these products.

Unlike Moskovich (1984), we do not think it is possible to tell whether a fragment has been produced by examining the remaining catheter. This is despite the fragments being single and, in some cases, as large as 370 mm^2. The size of the fragments is also likely to prevent them from being passed during voiding. Initially undetectable by ultrasound or X-ray, fragments will in time become encrusted by calcium deposits (Hukins *et al.*, 1983). This allows visualisation, but by then infections and irritative bladder symptoms may have developed.

In view of this, we consider that cystoscopy is mandatory following all cases of spontaneous catheter balloon rupture and after percutaneous balloon puncture to ensure that no free fragment remains in the bladder. The use of a flexible cystoscope or an integrated instrument such as the 17 F atraumatic cystourethroscope (Wolf) allows this to be done without incurring the additional risks of general anaesthesia.

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The Authors

J. M Chrisp, FRCS, FRACS, DipCommH, Senior Registrar, Department of Urology, Auckland Hospital.

J. N. Nacey, MD, FRACS, Consultant Urologist, Wellington Hospital; Senior Lecturer in Urology, Wellington School of Medicine, Wellington, New Zealand.

Requests for reprints to. J. M Chrisp, Department of Urology, Auckland Hospital, Park Road, Auckland 1, New Zealand

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Urinary Infection Following Out-patient Flexible Cystoscopy

K. R. CLARK and M. J. HIGGS

Department of Surgery, Queen Elizabeth Hospital, Gateshead

Summary—Of 161 flexible cystoscopies performed in an out-patient endoscopy suite, the incidence of urinary tract infection was 7.5%. Infection rates were higher in patients with a history of previous urinary tract infection or where an additional procedure was also performed. No difference was noted between the infection rates in men and women.

Diagnostic cystoscopies at this hospital were previously performed on an in-patient basis under general anaesthesia using a rigid cystoscope. With the development of the fully flexible cystoscope in 1982, however, the practice has changed.

Diagnostic cystoscopies using a flexible cystoscope were introduced to this hospital in 1987. They are performed under topical anaesthesia in an endoscopy suite which enables the procedure to be performed on an out-patient basis and requires minimal preparation and recovery time.

Although this practice is cost effective and more efficient for both surgeon and patient, we wished to know if the performance of an apparently lesser procedure carried an increased risk of infection to the patient. We therefore initiated a study to investigate the incidence of bacteriuria following out-patient flexible cystoscopy.

Patients and Methods

A total of 190 flexible cystoscopies were performed on 164 patients (48 female, 116 male) in an out-patient endoscopy suite. Mid-stream urine samples were collected from each patient before and 3 days after cystoscopy. The urethra was anaesthetised by the instillation of 15 ml of 2% lignocaine gel. External genitalia were prepared with povidone iodine and a split sterile towel isolated the operating area.

Both the Olympus and the Wolf flexible cystoscopes were used. Each instrument was sterilised by immersion in 2% activated glutaraldehyde (Cidex) 30 min before each session and for 10 min between each patient. Before use the endoscopes were washed with sterile water; 1.5% glycine was used for irrigation. The surgeon and assistant wore gowns and gloves but no masks were used.

Bacteriuria $>10^5$ organisms/ml was taken as evidence of urinary infection.

Statistical analysis

Results were analysed using the χ^2 test, with Yates correction and Fisher's exact test as indicated.

Results

In all, 29 samples were excluded: 8 (4%) were found to be infected prior to cystoscopy and 21 post-cystoscopy samples (11%) were unavailable for follow-up due to patients failing to provide a specimen.

There were therefore 161 evaluable results (139 patients) of which 12 (7.5%) showed no growth before cystoscopy and pure growths ($>10^5$ organisms/ml) 3 days after cystoscopy (Table 1). Table 1

Table 1 Infections in Men and Women 3 Days after Flexible Cystoscopy with a Clear Pre-cystoscopy Sample

	Female	*Male*	*Total*
No growth	33	116	149
Positive growth	4 (10 8%)	8 (6 5%)	12 (7 5%)
Total	37	124	161

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also shows the infection rate in women to be 10.8% (4/37) and in men 6.5% (8/124). This was not a statistically significant difference (χ^2 $P=0.47$).

Of the 12 positive samples only 3 growths (1.9%) were associated with pyuria (>10 pus cells/high powered field). The organisms involved are shown in Table 2.

Patients with a history of urinary tract infection (Table 3) were noted to have higher infection rates (Fisher's exact test $P<0.001$).

We also investigated the possibility that an additional procedure would influence the rate of infection. The procedures involved are shown in Table 4. Although the numbers were small, the results suggest that the performance of an additional procedure was a significant factor in producing a greater risk of infection (Fisher's exact test $P=0.002$).

We further analysed these figures to establish whether or not the performance of an additional procedure in a person with a history of previous urinary tract infection also increased the risk of infection. Table 5 shows that this was a significant factor in increasing the risk of infection (Fisher's exact test $P<0.001$).

There was only 1 positive growth after cystoscopy in patients with no history of urinary tract infection (Table 6) and so no definite conclusions could be drawn.

Table 2 New Infections after Flexible Cystoscopy

Organism	*No.*
Streptococcus faecalis	5
Escherichia coli	4
Coag. −ve staphylococcus	2
Proteus	1

Table 3 Cystoscopies and a History of Urinary Tract Infection

	No history	*Previous history*
No growth	125 (99.2%)	24 (68 6%)
Positive growth	1 (0.8%)	11 (31.4%)
Total	126	35

Table 4 Infections Following an Additional Procedure

	No growth	*Positive growth*
Additional procedure		
Biopsy	19	4
Diathermy	5	2
Urethral dilatation	2	2
Sub-total	26 (76 5%)	8 (23 5%)
No procedure	123 (96 1%)	5 (3 9%)

Table 5 Performance of an Additional Procedure in Patients with a History of Urinary Tract Infection

	No procedure	*Additional procedure*
Positive growth	4	7
No growth	21	0

Table 6 Performance of an Additional Procedure in Patients with no History of Urinary Tract Infection

	No procedure	*Additional procedure*
Positive growth	1	0
No growth	104	24

Discussion

The incidence of urinary tract infection following out-patient flexible cystoscopy is unknown. Fowler (1984) found 4 new infections in 39 patients (10%) although these patients did undergo both flexible and rigid cystoscopy under the same general anaesthetic.

We felt that an incidence of urinary tract infection of 7.5% following out-patient flexible cystoscopy was high. Similar studies using a rigid cystoscope by Richards and Bastable (1977), Fozard *et al.* (1983) and Manson (1988) produced infection rates of 4.5, 5.0 and 2.8% respectively. Comparison of our infection rate with these showed no significant difference (Fisher's exact test $P=0.46$).

The criterion for infection in the studies of Richards and Bastable (1977) and Fozard *et al.* (1983) required the presence of pus cells in addition to a pure growth. If this is applied to our study the rate of 7.5% becomes more acceptable (<2%). Manson (1988) obtained a lower infection rate (2.8%) but excluded patients requiring therapeutic intervention.

In contrast to the findings of Richards and Bastable (1977) and Fozard *et al.* (1983), we could not confirm a higher risk of infection in women but did confirm a higher risk to patients with a history of urinary tract infection. This study also suggests that the performance of an additional procedure led to a higher infection rate.

It was concluded that the performance of flexible cystoscopy in an out-patient endoscopy suite did not significantly increase the risk of bacteriuria and was therefore a safe procedure. In order to reduce our infection rate still further, we are organising a prospective trial of the selective use of prophylactic antibiotics.

The use of prophylactic antibiotics for diagnostic cystoscopy remains a contentious issue (Chodak and Plaut, 1979) but may be beneficial in high risk groups. The results of this study suggest that patients are at greater risk of infection if they have a history of urinary tract infection or if they undergo an additional procedure. Such patients may well benefit from prophylactic antibiotics.

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The Authors

K. R Clark, FRCS, Registrar in General Surgery, Department of Surgery, University of Newcastle upon Tyne

M. J Higgs, FRCS, Consultant Surgeon, Queen Elizabeth Hospital, Gateshead

Requests for reprints to: K R Clark, Department of Surgery, The Medical School, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH

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Origin and Structure of Benign Prostatic Hyperplasia

D. R. JONES, M. C. PARKINSON, G. J. GRIFFITHS, R. Ll. DAVIES and W. B. PEELING

Department of Diagnostic Radiology, University of Wales College of Medicine, Cardiff; St Peter's Hospitals, Institute of Urology, London; Department of Radiology, Royal Gwent Hospital and Department of Urology, St Woolos Hospital, Newport

Summary—The development of microradiography of the prostate gland has provided a new approach to investigating the origin and structure of benign hyperplasia. It has demonstrated that benign prostatic hyperplasia is usually microadenomatous in structure, although reticular types do occur. It originates at the lateral boundary of the periurethral muscle in the position of the transitional zone. In contrast, stromal nodules are homogeneous and amorphous in structure and develop at the site of the short straight urethral ducts within the periurethral muscle.

The anatomy of the prostate gland and the origin of benign prostatic hyperplasia have been a source of much debate and controversy.

In 1930, Lowsley described the periurethral glands as distinct from the prostatic lobes defined according to embryonic relationships. The extrapolation of these definitions into adult anatomy was unclear. Huggins and Webster (1948) divided the prostate into lobes according to oestrogen sensitivity and attributed benign hyperplasia to the anterior lobe. In 1954, Franks equated the periurethral glands of Lowsley with the inner glands of the prostate, which he distinguished from the remaining "true" prostate. He suggested that the inner glands were the site of origin of hyperplasia.

Current views are derived from detailed studies involving the examination of sagittal, parasagittal and coronal sections of the whole gland (McNeal, 1972, 1978, 1980) and have been reviewed by Blacklock (1982). It is proposed that the prostate consists of a wedge-shaped central zone which forms the base of the gland, its apex being the verumontanum. It sits in the cup-shaped peripheral zone which forms about two-thirds of the gland and constitutes the apex. The transitional zone also forms part of the "true" prostate and is composed of a system of glands lateral to the pre-prostatic sphincter, whose ducts run parallel to the urethra to enter it at the lower end of the sphincter. Periurethral glands which are not considered part of the true prostate have short straight ducts and are situated in the submucosa of the urethra within the cylinder of the preprostatic sphincter. Initially, McNeal (1972) suggested that benign hyperplasia arose from the periurethral glands (a view similar to that expressed by Franks (1954)). Following further study, he described the dominant glandular nodules of hyperplasia as arising in the transitional zone and the smaller nodules as more common in association with the periurethral glands (McNeal, 1978).

With the advent of X-ray microfocal units, tissue structure can be investigated and this has been applied to the prostate gland (Davies *et al.* 1988; Jones *et al.*, 1989). In this study the site of origin and structure of benign hyperplasia was investigated by comparison of microradiographs and corresponding histopathology in cadaver prostates.

Materials and Methods

The technique has been subject of an earlier report (Jones *et al.* (1989) and is described only briefly here. The cadaver prostates were initially fixed in formalin for 3 days. They were sectioned transversely every 0·5 cm; 1-mm sections were taken and freeze dried prior to microradiography and adjacent sections taken for histopathology and prepared with routine haematoxylin and eosin staining.

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The corresponding microradiographs and sections were compared. In previous microradiographic studies, 4 types of structure (amorphous, regular, microadenomatous and reticular) have been identified in the prostate gland (Davies *et al.*, 1988). The distribution of each pattern in the microradiographs was independently recorded. The histopathological sections were also independently mapped to delineate benign tissue and 2 forms of hyperplastic nodules in which either glands ("adenoma") or stroma (stromal nodule) predominated. The corresponding sections were then compared to investigate the microradiographic features and site of these 2 forms of benign hyperplasia.

Results

A total of 100 cadaver prostates were examined, of which 71 were shown to be benign and entered into this study (age 17–86 years); 15 glands were normal (age range 17–72) and the remaining 56 glands were hyperplastic (age range 49–86) (Table).

The normal gland (Fig. 1) consisted of an amorphous or regular structured periurethral zone which had a distinct edge adjacent to the glandular tissue. On comparing microradiographs and H and E sections, this periurethral zone proved to be muscle. Within the periurethral muscle were seen the short periurethral ducts. The central zone had a coarse reticular structure while the peripheral zone had a fine reticular structure.

Examination of the periurethral zone showed that there were 2 distinct sites where benign lesions occurred (Fig. 2). In 54 cases the distinct edge of the periurethral muscles was obliterated by single (6 cases) or multiple (48 cases) small rounded masses ("microadenomata" and "macroadenomata") (Figs. 2 and 3). Three of these lesions at this site had a reticular architecture and histopathology showed them to be typical benign hyperplastic glandular nodules. They were not surrounded by periurethral muscle. Their site of origin coincided with the position of the description given from McNeal's transitional zone (McNeal, 1980).

Table Examination of Cadaver Prostates

	No.
Normal prostates	15
Reticular nodules	3
Microadenomatous nodules	39
Stromal and microadenomatous nodules	12
Stromal nodules	2
Total	71

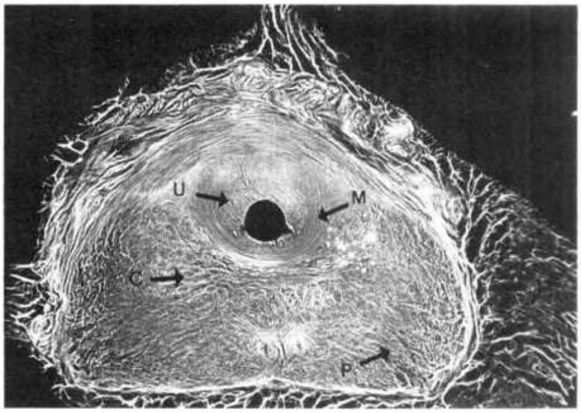

Fig. 1 Structure of the normal gland. C = central zone (coarse reticular structure). P = peripheral zone (fine reticular structure). M = periurethral muscle. U = short urethral ducts.

Hyperplastic lesions were also seen to arise from within the periurethral zone (Fig. 2) in 14 prostates, 12 in association with microadenomatous hypertrophy. The structure was different from that of the more common type of hyperplasia described above as it was uniformly amorphous and surrounded by periurethral muscle (Fig. 4). The corresponding H and E section showed stromal nodules. Their origin was therefore from the connective tissue associated with the short straight urethral ducts within the periurethral muscle.

Discussion

In his histopathological study of 63 autopsy pros-

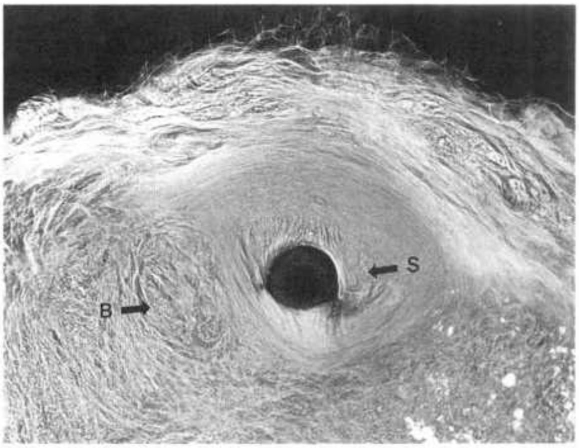

Fig. 2 Development of benign adenomas. B = benign prostatic hyperplasia (developing adenoma); microadenomatous structure. S = stromal nodule developing.

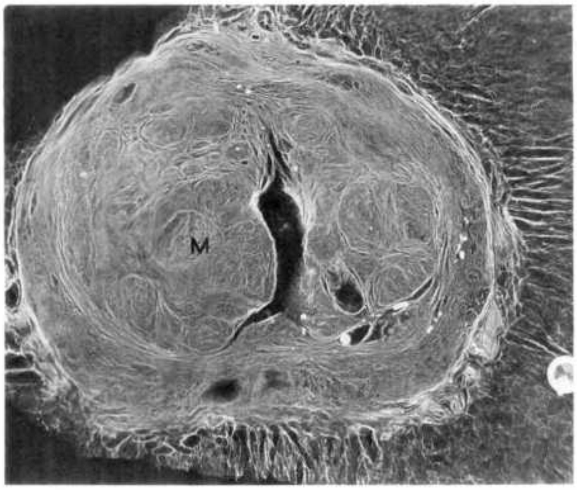

Fig. 3 Microadenomatous benign hyperplasia. M = microadenomatous nodule.

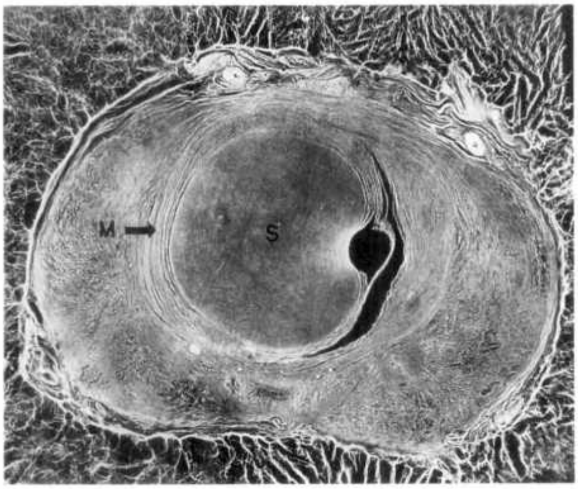

Fig. 4 Stromal nodule. S = stromal nodule. M = periurethral muscle.

tates, McNeal (1978) found that the common glandular form of hyperplasia arose from the transitional zone, whereas stromal nodules were associated with the periurethral short ducts. That both of these areas contribute to benign hyperplasia may reflect their common embryological derivation (Blacklock, 1982). The results of this microradiographic and histopathological study of 71 cadaver prostates supports McNeals' findings and shows that they have a different internal structure.

The clinical significance of these findings relates to the interpretation of the ultrasonic findings. The microadenomas result in mid-range ultrasonic echoes, whereas the periurethral muscle and stromal nodules, having an amorphous structure, cause low range ultrasonic echoes.

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The Authors

D. R. Jones, FRCSE, formerly Research Fellow, Department of Diagnostic Radiology, University of Wales College of Medicine. Now Urological Registrar, General Infirmary, Leeds.

M. C. Parkinson, BSc, MD, FRCPath, Consultant Histopathologist, St Peter's Hospitals, Institute of Urology.

G. J. Griffiths, MD, FRCR, Consultant Radiologist, Royal Gwent Hospital.

R. Ll. Davies, MSc, PhD, MIBiol., CBiol., Senior Research Officer, Department of Diagnostic Radiology, University of Wales College of Medicine.

W. B. Peeling, MA, FRCS, Consultant Urological Surgeon, St Woolos Hospital.

Requests for reprints to: D. R. Jones, 25 Robin Chase, Robin Lane, Pudsey, West Yorkshire LS28 7DH.

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Antibiotic Compared with Antiseptic Prophylaxis for Prostatic Surgery

S. PRESCOTT, M. A. HADI. R. A. ELTON, A. W. S. RITCHIE, G. C. FOUBISTER, J. C. GOULD and T. B. HARGREAVE

Department of Surgery/Urology and Central Microbiological Laboratories, Western General Hospital; Medical Statistics Unit, University Medical School, Edinburgh

Summary—Two different regimens of cephalosporin antibiotic prophylaxis were compared with antiseptic lubricating jelly to try to prevent infection and complications in 196 men after prostatic surgery. Pre-operative urine was cultured and prostatic chips (170 cases) were also cultured to define the source of any infection. The use of antibiotics was associated with a reduced risk of post-operative bacteriuria. No serious complications occurred, although 1 patient in the antiseptic treated group developed rigors; 79 of 170 patients (46%) had positive prostatic chip cultures, of whom 74 had sterile pre-operative urine. There was no association between the result of chip culture and the presence of a pre-operative catheter. Culture positive patients had an increased risk of post-operative urine infection, although the same organism was found in the prostate and urine in only 36% of cases of post-operative bacteriuria and in 43 (54%) the organism cultured from the prostate was *Staphylococcus albus*. This study provides further evidence of the benefit of true prophylactic antibiotic therapy for transurethral prostatic surgery and the prostatic chip data suggest that some of the risk is due to pre-operative contamination of the prostate in the absence of per-operative urinary infection or catheterisation.

Transurethral resection of the prostate is the commonest operation performed on men over the age of 65 years and has a low morbidity and peri-operative mortality rate of less than 1% (Murphy *et al.*, 1983). Whilst the majority of deaths that do occur are due to unavoidable cardiovascular complications, there are a number of men who die from avoidable septicaemic shock. The incidence of septicaemia is 0 to 4%, although 10 to 32% will have a transient bacteraemia (Grabe, 1987). There is little debate about the need for antibiotic prophylaxis in patients who are known to have a pre-operative bacteriuria. However, only 10% of urologists in the United Kingdom routinely give antibiotics to all patients undergoing TURP (Wilson and Lewi, 1985). The most commonly cited reasons for not giving prophylaxis are the generally low level of infective complications, lack of proof of efficacy, cost and the possibility of selecting antibiotic resistant strains of bacteria. We have shown in a randomised control trial involving a group of patients without known pre-operative urinary infection undergoing TURP, that 48 hours of peri-operative parenteral cefotaxime resulted in a significant reduction in morbidity and mortality, including shorter hospitalisation when compared with no treatment (Hargreave *et al.*, 1982). Moreover, this regime was significantly more effective than a single pre-operative dose (Hargreave *et al.*, 1984), which is in agreement with other series (Grabe, 1987). In addition, the use of broad spectrum cephalosporins during a continuous 5-year period did not result in the emergence of any new bacterial resistance patterns (Bentsi *et al.*, 1987).

Between 6 and 70% of patients with pre-operative sterile urine will develop significant bacteriuria post-operatively (Grabe, 1987). Unless the organism is *Staphylococcus albus*, urinary bacterial counts of 10^3 organisms/ml progress to significant

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infection within 4 days (Gordon *et al.*, 1983). The sources of post-operative bacteraemia in patients with previously uninfected urine may be several. Skin or urethral bacteria may be introduced into the circulation directly from the urethra by instrumental or catheter trauma or indirectly following colonisation of the urine. This may occur at the time of surgery or afterwards, particularly via the catheter lumen if accidental breaks of the closed drainage system occur or the catheter needs to be unblocked. Finally, it has been shown that quantitatively the most important factor associated with bacteraemia is positive culture from resected prostatic tissue, frequently in the presence of negative urinary culture (Robinson *et al.*, 1982).

The aims of the present randomised study were 3-fold:

1. To compare the use of prophylactic antibiotic treated groups with pre-operative lubrication of the urethra and all instruments with antiseptic jelly containing chlorhexidine.
2. To assess further the prognostic value of culture of prostatic chippings from patients with negative urine culture at the time of surgery.
3. To compare the effectiveness of 48 hours' treatment with parenteral cefotaxime with a similar course of another third generation broad spectrum cephalosporin, ceftizoxime.

Patients and Methods

All patients undergoing transurethral prostatic surgery were eligible for entry to the trial with the following exclusions; those with known pre-operative bacteriuria, those already receiving antibiotic therapy and those who had a history of allergy to penicillins or cephalosporins. We also excluded patients with severe renal or hepatic failure. Some patients had bacteriuria prior to surgery but this was not known until afterwards. We have included these patients in our analysis. All patients gave informed consent before participating in the study.

The patients were divided into 2 groups: those with and those without a urinary catheter pre-operatively. Each group was randomised separately to receive 1 of the following regimes:

1. Intravenous cefotaxime 1 g pre-operatively, followed by 3 further intramuscular doses at 12-hourly intervals.
2. Intravenous ceftizoxime 1 g pre-operatively, followed by 3 further intramuscular doses at 12-hourly intervals.
3. Lubrication of the urethra with sterile petroleum jelly containing 0.5% chlorhexidine 5 min prior to instrumentation, with lubrication of all instruments, including the catheter, with the same jelly.

The patients in the first 2 groups received KY jelly as lubricant for all instruments but in all other respects all 3 groups were treated similarly. The operative technique was standardised as far as possible, although the operations were performed by different surgeons. If urethral dilatation was required the Otis was used and this fact recorded. During the procedure a glycine solution was used to irrigate the bladder. After completion of resection a 3-way Foley catheter was inserted and continuous irrigation with saline used until haemostasis was adequate.

Details of the operation and daily clinical progress were recorded on special pro-formas. At the time the clinical recordings were made the doctor making the recordings was unaware to which treatment regimen the patient was allocated. Recatheterisation was necessary when a patient was not able to void either after removal of the catheter or when a catheter had become blocked by blood clots. Continence problems refer to temporary incontinence lasting for more than 24 h after removal of the catheter; dysuria was recorded only if symptoms persisted for more than 24 h after removal of the catheter. Fresh urine samples in the form of mid-stream samples or aspirates from the catheter tubing were sent prior to surgery and daily afterwards until the day of discharge or tenth post-operative day. These samples were specially identified and handled separately by the bacteriology department. They were examined microscopically and cultured using a quantitative technique. Isolates were identified and sensitivity tests to a range of commonly used antibacterial agents in addition to cefotaxime and ceftizoxime were carried out.

Prostatic chips were collected aseptically at operation and transferred to dry sterile containers for immediate despatch to the laboratory. The chips were shaken vigorously in broth for 30 min and aliquots of the broth plated for culture. The remaining chips were then incubated in the broth overnight. Colony counts were made on the incubated plates and the organisms identified and tested for their antibiotic sensitivity as above.

Blood samples for haemoglobin and white cell count and urea and electrolytes were taken both pre- and post-operatively. Blood cultures were taken when appropriate.

A 2-stage analysis of the results was performed, firstly comparing cefotaxime with ceftizoxime and then antibiotics against antiseptic jelly. Statistical analysis was carried out by χ^2 tests or Wilcoxon rank sum tests as appropriate.

Results

The study group included 196 patients. Of these, 64 patients received cefotaxime, 67 received ceftizoxime and 65 received topical antiseptic jelly. The groups were well balanced for age, indication for surgery, the presence of a pre-operative catheter or unknown pre-operative bacteriuria and also for routine haematological and biochemical parameters (Table 1). There were also no differences in the operative details between the groups (Table 2) or in the rates of immediate complications in the recovery room such as hypotension, clot retention and bladder washout.

Table 1 Pre-operative Details

	Patient group		
	Antiseptic ±SD (%)	*Ceftizoxime ±SD (%)*	*Cefotaxime ±SD (%)*
Age (years)	71±8	71±8	69±10
Indications BPH	51 (79)	56 (84)	55 (86)
Cancer	10 (15)	11 (16)	7 (9)
BN	2 (3)	2 (3)	2 (3)
Pre-op catheter	13 (20)	14 (21)	14 (22)
Unknown +ve MSSU	2 (3)	3 (4)	3 (4)
Haemoglobin (g/dl)	14.1±1 7	14.5±2 0	14 3±1 4
WCC (×10^9/l)	8 0±2.4	8.0±2 3	8 0±2 6
Urea (mmol/l)	6 9±3 0	6 4±3 3	6 8±3.0
Sodium (mmol/l)	140.8±3 7	140 9±3.4	141 3±3.1

BN = Bladder neck

Table 2 Operative Details

	Patient group		
	Antiseptic ±SD (%)	*Ceftizoxime ±SD (%)*	*Cefotaxime ±SD (%)*
No grammes resected	24±24	29±46	29±48
Units blood transfused	0 2±0.7	0.3±1 1	0.1±0 3
Size of sheath (F)	25.6±1 3	25 6±1.4	25 9±1.4
Use of Otis	19 (31)	17 (26)	23 (37)
Size of catheter (F)	22.1±0 9	22.0±0.2	21 9±1.0
Duration of op. (min)	40±38	39±16	35±17
Immediate post-operative complications			
Hypotension	6 (9)	8 (12)	4 (7)
Clot retention	7 (11)	6 (9)	4 (7)
Bladder washout	12 (19)	10 (15)	7 (13)

Table 3 shows comparative post-operative progress and complications for the 3 groups. There was no significant difference either for the overall incidence of post-operative complications or for any of these taken individually. The antiseptic treated patients required significantly more additional antibiotic therapy than the other groups during their admission ($P<0.05$).

Ceftizoxime treated patients had a significantly lower morning temperature than either cefotaxime ($P<0.05$) or antiseptic ($P<0.01$) treated patients (Table 4). Also, the antibiotic treated groups combined had a significantly lower maximum post-

Table 3 Post-operative Progress

	Patient group		
	Antiseptic ±SD (%)	*Ceftizoxime ±SD (%)*	*Cefotaxime ±SD (%)*
Discharge day	5 7±2.3	5 8±2 1	5.2±1.6
Complications	20 (31)	21 (31)	11 (17)
Rigors	1 (2)	—	—
Bacteraemic shock	—	—	—
Orchitis	—	2 (3)	—
Chest infections	—	1 (1)	—
Hypotension	—	1 (1)	1 (2)
Skin rash	—	1 (1)	—
GI upset	2 (3)	3 (4)	1 (2)
Temporary incontinence	11 (17)	9 (13)	3 (5)
Bladder washout	6 (9)	8 (12)	6 (9)
Clot retention	3 (5)	3 (4)	—
Catheter days *in situ*	2 5±1.1	2 6±0.9	2 5±0.9
Additional antibiotics	6 (9)	1 (1)	2 (3)*
Any blood transfused	4 (6)	6 (9)	3 (4)

*Antiseptic > antibiotic (CTZ+CTX) $P<0\ 05$

Table 4 Post-operative Monitoring

	Patient group		
Maximum and minimum values	*Antiseptic ±SD (%)*	*Ceftizoxime ±SD (%)*	*Cefotaxime ±SD (%)*
Max temp am*	37 1±0 49	36.9±0 43	37 1±0 49
Max temp pm	37 2±0 53	37 1±0 40	37 1±0.48
Max pulse am	84±11	85±11	84±13
Max pulse pm	84±9	85±10	82±10
Min Hb (g/dl)	12 1±2 0	12 1±2 2	12 6±1.6
Max WBC (×10^9/l)	11 0±3.2	9.9±3 4	9.4±3.1
Max urea mmol/l	6 1±3 6	5.7±4 2	5.7±2 9
Max sodium (mmol/l)	138 9±3 9	140 1±4.3	140.1±3.6

*Ceftizoxime significantly lower than cefotaxime ($P<0\ 05$) and antiseptic ($P<0\ 01$).

operative white cell count compared with the antiseptic group ($P<0.01$). The results in Table 5 refer to the maximum count of organisms/ml in post-operative urine samples and statistical analysis is by the Wilcoxon rank sum test. Overall, 15 of 196 cases (7.7%) had a maximum count of $\geqslant 10^6$/ml and 38 additional cases (19.4%) had a maximum count of $\geqslant 10^3$ organisms/ml. There was a significant reduction in positive counts of $\geqslant 10^6$ organisms/ml in the antibiotic treated compared with antiseptic treated patients for any organism ($P<0.001$), *Escherichia coli* ($P<0.001$) and *Enterococci* ($P<0.01$). There were also 5 cases in which *Staph. albus* was cultured from ceftizoxime but not from cefotaxime treated patients ($P<0.05$).

Blood cultures were performed in only 9 patients: 6 in the antiseptic group, 2 in the ceftizoxime and 1 in the cefotaxime groups. Four positive results were achieved from the 6 in the antiseptic group (*Staph. albus* 2, *Proteus mirabilis* 1 and *Streptococcus faecalis* 1) but none from the antibiotic groups.

Prostatic chip culture data were available on 170 patients and positive results in 79 patients (46%) indicated titres of $\geqslant 10^3$ organisms/g tissue (Table 6). Of the 74 pre-operative urine culture negative/prostatic chip culture positive cases, 41 (55%) grew *Staph. albus*, followed by *E. coli* 10 (13%), *Enterococcus* 6 (8%), *Staph. aureus* 5 (7%) and coliforms 7 (9%). It was the *Staph. albus* group which accounted for the significantly fewer positive cultures obtained in the ceftizoxime group compared with the cefotaxime group ($P<0.05$). There was also a significant reduction in positive cultures for *Proteus* ($P<0.01$), coliforms ($P<0.05$) and any organism ($P<0.05$) in the combined antibiotic treated groups compared with the antiseptic jelly treated group. There was no significant correlation between the presence of a pre-operative urinary catheter and the presence of a positive chip culture for any organism. In particular, *Staph. albus* was found in 13/36 patients (36%) with catheters and 29/132 patients (21%) without catheters, a difference which was not significant.

Table 5 Maximum Titre of Organisms in Post-operative Urine Samples

	Antiseptic		*Ceftizoxime*		*Cefotaxime*	
Organism	$\geqslant 10^6$	$\geqslant 10^3$	$\geqslant 10^6$	$\geqslant 10^3$	$\geqslant 10^6$	$\geqslant 10^3$
*E. Coli**	8(12)	15(23)	1(1)	1(1)	1(2)	3(5)
Klebsiella	1(2)	1(2)	—	—	—	—
Pseudomonas	1(2)	1(2)	—	—	1(2)	1(2)
Proteus	1(2)	1(2)	—	1(1)	1(2)	1(2)
Coliforms	—	—	—	1(1)	—	1(2)
Enterococcus†	1(2)	4(6)	—	—	—	—
Staph. aureus	—	1(2)	—	—	—	—
Staph albus‡	—	2(3)	—	5(7)	—	—
Yeast	1(2)	1(2)	—	1(1)	—	1(2)
Streptococcus	—	—	—	—	—	—
Any organism§	12(18)	24(37)	1(1)	9(13)	2(3)	5(8)

Antiseptic v antibiotic *$P<0.001$, †$P<0.01$, §$P<0.001$.
Cefotaxime v ceftizoxime ‡$P<0.05$.

Table 6 Culture Results from Resected Prostatic Chippings

	Antiseptic		*Ceftizoxime*		*Cefotaxime*	
Organism	$\geqslant 10^6$	$\geqslant 10^3$	$\geqslant 10^6$	$\geqslant 10^3$	$\geqslant 10^6$	$\geqslant 10^3$
E. coli	—	6(11)	—	1(2)	—	5(9)
Klebsiella	—	—	—	—	—	1(2)
Pseudomonas	—	1(2)	—	—	—	1(2)
*Proteus**	1(2)	4(7)	—	—	—	—
Coliforms†	—	5(9)	—	1(2)	—	1(2)
Enterococcus	—	2(3)	—	3(5)	—	2(3)
Staph aureus	—	3(5)	—	1(2)	—	1(2)
Staph albus‡	—	13(23)	—	8(15)	—	22(38)
Yeast	—	—	—	—	—	—
Corynebacterium	—	—	—	—	—	—
Streptococcus	—	1(2)	—	1(2)	—	2(3)
Pneumococcus	—	1(2)	—	—	—	—
Any organism§	1(2)	32(56)	—	15(27)	—	32(55)

Cefotaxime v ceftizoxime ‡,§$P<0.05$
Antiseptic v antibiotic *$P<0.01$, †,§$P<0.05$

The same organism was found in the prostatic chip in only 1 of the 8 patients with a positive pre-operative urine culture. Of the 170 patients in whom prostatic chip culture was performed, 32 went on to develop positive post-operative urine cultures. A positive prostatic chip culture gave a significantly higher risk of developing a post-operative bacteriuria (22/79 patients: 28%) compared with negative culture (10/91: 11%) using the χ^2 test ($P<0.01$, $\chi^2=7.9$) (Table 7). The same organism was cultured from both prostatic chips and urine in 8/32 post-operative bacteriurias (25%) and 8/22 (36%) of these who had positive prostatic chip cultures. However, in 57/79 positive chip culture patients (72%) no bacteriuria resulted (although 47 had received a prophylactic course of antibiotics).

The sensitivity and resistance patterns of the organisms cultured from both urine and prostatic chips were examined. The organisms in 32 of the 39 positive urine samples (82%) were sensitive to both of the antibiotics used in the study. There was only 1 case in which an organism was sensitive to 1 but not the other (ceftizoxime-sensitive). There was no difference in the sensitivity pattern between the

Table 7 Comparison of Prostatic Chip Culture with Post-operative Urine Culture Results

	Urine culture				
	Pre-operative		*Post-operative*		
Prostatic chip culture	*Negative*	*Positive*	*Negative*	*Positive*	
				Same	*Different*
Negative	89	2	81	0	10
Positive	74	5	57	8	14
Total	163	7	138	8	24

3 groups of patients. The spectrum of activity was examined in the prostatic chips from 78 patients and in 71 cases (91%) the organisms were sensitive. Again, there was no difference in pattern between the 3 groups.

Discussion

There is controversy about whether antibiotics should be administered to patients undergoing transurethral prostatectomy in the true prophylactic situation, *i.e.* when pre-operative urine cultures are negative, and therefore our study included a comparison group who received only antiseptic jelly. The rationale for the use of antiseptic jelly is that it should reduce the risk of introduction of organisms into the urinary tract at the time of surgery, although it obviously would not clear organisms which had already colonised the tissues or prevent organisms gaining entry post-operatively. The duration of the antibiotic cover (48 h) was designed to cover the post-operative period during which a urinary catheter was *in situ*. The study also included culture of the prostatic chippings as well as pre-operative urine culture to give more information about organisms that were already within the urinary tract. In common with the majority of larger series, this study showed that there was a significant reduction in post-operative bacteriuria and the associated elevation of temperature and white blood cell count which accompanied this as a result of prophylactic antibiotic therapy for patients with a negative pre-operative urine culture undergoing transurethral resection of the prostate (Grabe, 1987).

Our previous studies (Williams *et al.*, 1980; Hargreave *et al.*, 1982, 1984; Bentsi *et al.*, 1987), have not only shown a reduction in post-operative bacteriuria from the use of antibiotics but have also demonstrated significant benefit in terms of reduction in post-operative morbidity and in-patient stay. The present study failed to demonstrate any benefit from prophylactic antibiotic therapy on these criteria when compared with antiseptic therapy. There are several possible reasons for this. Firstly, the group of patients was of lower infective risk than in our previous studies in that the percentage of patients with an unknown positive pre-operative urine culture was low at 4% (compared with 28% in 1980, 12% in 1982, 8% in 1984 and 9% in 1987) and the percentage with a pre-operative catheter was also low at 21% (compared with 37% in 1980, 20% in 1982, 31% in 1984 and 31% in 1987). This is reflected in the low post-operative rates of significant bacteriuria ($\geqslant 10^6$ organisms/ml) of 18% in the antiseptic and 2% in the antibiotic treated groups. It is also possible that the use of antiseptic prophylaxis does exert some benefit, thus reducing the difference in complication rates between the 2 groups.

The 2 cephalosporins used in the trial, ceftizoxime and cefotaxime, appear to be suitable for single agent prophylaxis in prostatic surgery with the organisms cultured from 32 of 39 (82%) positive post-operative urines and 71 of 78 (91%) positive prostatic chippings sensitive to both. Cephalosporins have been routinely used in this unit for over 8 years and there has been no sign of the emergence of resistant strains of organism.

The work of Robinson *et al.* (1982) suggested that the prostate itself was the commonest source of the organisms causing post-operative bacteriuria and that the presence of a pre-operative urinary catheter was a significant risk factor for this. As in our study, the commonest organism that they isolated was *Staph. albus*. This organism is not usually considered to be a pathogen in the urinary tract and the method of colony counting used in our study does not completely exclude contamination of the chips as a cause of the positive results. Whilst both prostatic chippings and post-operative urine culture grew organisms of the same type in only 8 of the 22 cases (36%) in which both were positive, we found that the presence of a positive prostatic chip culture (any organism $\geqslant 10^3$ organisms/g) was associated with a significantly higher risk of post-operative bacteriuria. Furthermore, we were unable to show that a pre-operative catheter increased the chance of positive culture from the prostate. These facts taken together suggest that the increased risk of a significant post-operative bacteriuria predicted by the positive prostatic chip culture is a reflection of contamination of the urinary tract at the time of surgery. The significant reduction in positive cultures from the prostatic chippings in the antibiotic compared with the antiseptic treated group could be explained by rapid accumulation of these drugs within the gland (they were only administered at induction of anaesthesia), which was then sufficient to prevent subsequent growth of organisms in culture.

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The Authors

S Prescott, FRCSE, Lecturer in Urology.

M A. Hadi, MD, Professor of Urology, Dhaka Medical College, Bangladesh.

R. A. Elton, PhD, Senior Lecturer in Medical Statistics

A. W. S. Ritchie, MD, FRCSE, Senior Lecturer in Urology

G C. Foubister, FRCSE, Registrar in Urology

J. C. Gould, MD, FRCP, FRCPath, formerly Director, Central Microbiological Laboratories.

T B Hargreave, MS, FRCS, Senior Lecturer and Honorary Consultant Urological Surgeon.

Requests for reprints to: S. Prescott, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU.

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Radiotherapy for Palliation of Locally Advanced Prostatic Carcinoma

H. G. KYNASTON, C. W. KEEN and P. N. MATTHEWS

Department of Urology, University Hospital of Wales; South Wales Radiotherapy and Oncology Service, Velindre Hospital, Cardiff

Summary—Some patients present with distressing symptoms due to locally advanced prostatic carcinoma which may be refractory to hormonal manipulation and/or surgical treatment. Over an 8-year period 26 patients received local palliative radiotherapy for recurrent bleeding and lower urinary outflow tract obstruction. All were treated with conventional external beam radiotherapy and all but 2 obtained useful palliation of symptoms, especially those with recurrent bleeding. We also found that radiotherapy could be given to the majority of patients on an out-patient basis in 2 or 3 fractions. This was well tolerated and there were few side effects.

Many patients present with locally advanced prostatic carcinoma. Urinary outflow tract obstruction in such patients is generally treated by hormonal manipulation, with transurethral resection also playing a palliative role (Javadpour, 1979). Recurrent bleeding due to carcinoma of the prostate (which occurs in up to 45% of patients) can sometimes be controlled by endoscopic resection or fulguration (Tomlinson, 1977). However, in spite of these measures patients may suffer recurrent symptoms where further surgery is either unsuccessful or contraindicated due to the general condition of the patient. The life expectancy of such patients is limited and effective palliation of distressing local symptoms should be the aim of treatment. The role of radiotherapy in this particular situation has not been well documented, although 2 previous reports have suggested the benefit of radiotherapy in local symptom control (Kraus *et al.*, 1972; Fossa, 1987).

We now report our experience in achieving clinical control in patients with locally advanced tumours receiving palliative radiotherapy at the South Wales Radiotherapy Centre.

Patients and Methods

All patients referred for palliative radiotherapy in order to improve urinary symptoms due to locally advanced prostatic carcinoma during the period 1980 to 1988 were reviewed. Twenty-six patients were treated (mean age 73 years, range 53–87). The main symptoms requiring treatment were related to outflow tract obstruction and recurrent haematuria (Table). All patients had previously been treated by hormonal manipulation and 17 had undergone transurethral resection on at least one occasion. They were treated as in-patients or out-patients according to the number of fractions given and the distance between their home and the hospital.

Radiotherapy was given by means of a parallel opposed pelvic pair and field sizes ranged from 12 × 12 to 12 × 15 cm with 10 MV photons from a linear accelerator. Two fractionation schemes were used. The first consisted of daily fractions of 233 cGy, usually to a tumour dose of 3500 cGy in

Table Symptoms of Locally Advanced Prostatic Carcinoma

Symptoms	*No of patients (%)*
Voiding difficulty	13 (50)
Recurrent haematuria	9 (35)
Recurrent haematuria + voiding difficulty	4 (15)
Total	26

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15 fractions over 3 weeks; occasionally 18 fractions were given. The second scheme comprised 3 fractions of 800 cGy tumour dose, with an interval of 7 days between fractions 1 and 2 and 2 weeks between fractions 2 and 3 (0-7-21 technique). If adequate palliation was achieved earlier, the final fraction(s) were not given.

Results

Patients were divided into groups according to the 2 major symptoms of obstruction and haematuria. Symptoms due to outflow tract obstruction were graded 0–3, according to the severity of symptoms, and the response to palliative radiotherapy is shown in Figure 1. Symptoms due to obstruction improved in 15 of the 17 patients (88%), with 10 of the 12 catheterised patients no longer requiring a catheter. Nine patients progressed to grade 1 and 5 patients became asymptomatic. The end point of useful palliation was defined as a recurrence or worsening of symptoms or death of the patient. Half of the patients with obstructive symptoms maintained symptomatic improvement at 11 months (range 5–24). Of the 2 patients who failed to respond, 1 was unable to void following a trial without catheter and the other died from a pulmonary embolus during treatment.

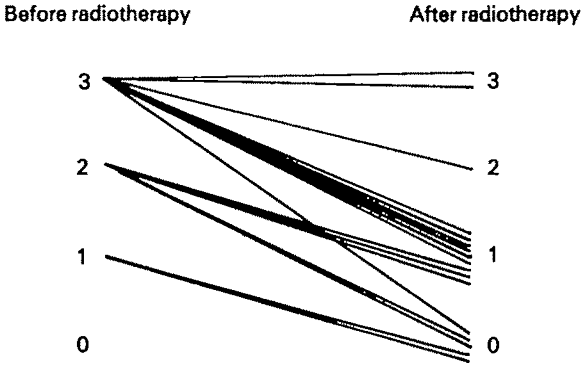
Patients with recurrent haematuria were also graded 0–3 and their response to palliative radiotherapy is shown in Figure 2. All responded to treatment. Eleven of the 13 patients became asymptomatic following a single course of radiotherapy. One relapsed 4 months after treatment but responded to 2 further fractions of 800 cGy and the other patient suffered mild recurrent haematuria.

Toxicity was not a major problem. With the daily fractionation scheme some degree of proctitis and diarrhoea occurred, corresponding to WHO grade 1 or 2 toxicity. This always responded to symptomatic treatment with loperamide and in no case was it necessary to interrupt treatment. With the 0-7-21 technique, bowel reaction was not a problem, although 1 patient showed mild erythema with no desquamation. There were no long-term side effects from either treatment.

The daily fractionation scheme is now used for patients with outflow obstruction unless the patient is frail and/or lives at a distance, in which case the 0-7-21 technique is used. Patients with haematuria are treated with the 0-7-21 technique, usually with a field size of 12 × 12 cm. Approximately 50% of patients will stop bleeding after the first fraction.

Discussion

Radiotherapy gives useful palliation in the treatment of bony metastases due to prostatic carcinoma (Hope-Stone, 1980) and may relieve ureteric ob-



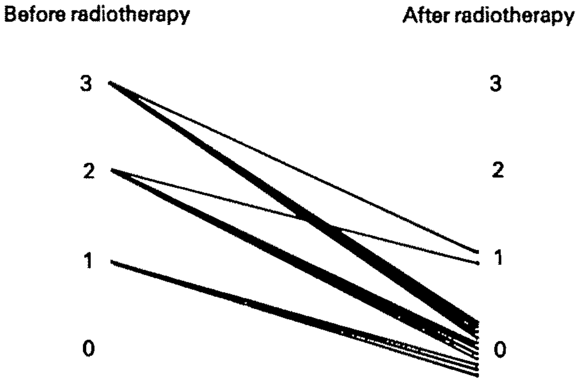
0 = No symptoms.

1 = Poor stream, frequency 6–10 times, nocturia <4 times.

2 = Dribbling, poor control, nocturia >4 times.

3 = Retention requiring catheterisation.

Fig. 1 Grading of symptoms and results of radiotherapy for the 17 patients with voiding difficulty.



0 = Asymptomatic.

1 = Haematuria <1 per day.

2 = Haematuria >1 per day.

3 = Clot retention (or sufficient to cause haemoglobin to fall).

Fig. 2 Results of radiotherapy for the 13 patients with haematuria.

struction (Fossa, 1987). Radical radiotherapy to the prostate has been used extensively in patients with early prostatic carcinoma in an attempt to cure the disease (Bagshawe and Ray, 1983; Dobbs *et al.*, 1985; Schellhammer *et al.*, 1985). However, its use as a palliative measure in order to control distressing symptoms due to advanced local disease has received scant attention in the literature. Gibbons *et al.* (1979) found that 90% of patients with stage C carcinoma of the prostate treated with external beam radiation therapy did not require a later prostatic operation for obstruction and the incidence of haematuria was less than that reported in non-irradiated patients. Kraus (1972) reported that haematuria in 13 patients ceased with radiotherapy, but some patients started hormonal therapy at the same time as radiation treatment. The majority of our patients obtained worthwhile palliation of symptoms. The essence of any palliative treatment is that it should be effective, simple and, if possible, devoid of side effects. We came close to achieving this in the patients with haematuria. Over half of them stopped bleeding after a single out-patient dose of radiotherapy, while the remainder required only a further 1 or 2 out-patient sessions.

We have not used the above regime in patients with urinary retention because many "trials without catheter" would be required to assess the response to radiotherapy. All patients who were treated for retention of urine due to locally advanced tumours received 15 to 18 fractions over 3 to 4 weeks (3500–4161 cGy). Eight such patients voided 3 to 5 weeks after the course of treatment. We now recommend a course of 15 fractions over 3 weeks (3500 cGy) in catheterised patients, with a trial without catheter 3 weeks later. Hope-Stone (1980) suggested 4000 cGy in 4 weeks with parallel opposed fields in undifferentiated tumours as a palliative measure, but did not state whether this was for specific symptoms or in order to reduce the incidence of local symptoms.

Prostatic stents inserted under topical anaesthesia have been used in elderly patients with prostatic obstruction unsuitable for surgery (Williams *et al.*, 1989) but the possibility that stents will offer relief of obstruction or haematuria due to prostatic carcinoma has still to be evaluated.

This study shows that the majority of patients with symptoms due to locally advanced cancer of the prostate can obtain very effective palliation from local radiotherapy.

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The Authors

H. G Kynaston, FRCS, formerly Surgical Registrar, Department of Urology, University Hospital of Wales. Now Urology Research Registrar, Royal Liverpool Hospital

C W Keen, FRCP(C), Consultant Radiotherapist, Velindre Hospital

P N. Matthews, FRCS, Consultant Urologist, University Hospital of Wales.

Requests for reprints to· H. G Kynaston, Department of Urology, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP

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Serum Levels of Sex Hormone Binding Globulin and Oestradiol in Patients with Testicular Cancer

SOPHIE D. FOSSÅ and E. HAUG

Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital; Hormone Laboratory, Aker Hospital, Oslo, Norway

Summary—Serum testosterone (T), oestradiol (E–2) and sex hormone binding globulin (SHBG) were measured in 84 orchiectomised testicular cancer patients before further treatment and 4 to 6 and 12 to 15 months after therapy. Patients were divided into 3 groups according to treatment: *Group 1*: cisplatin-based chemotherapy (27 patients); *Group 2*: abdominal radiotherapy (32 patients); *Group 3*: no antiproliferative treatment (chemotherapy/radiotherapy) (25 patients). Between 4 and 6 months after antiproliferative treatment, particularly after chemotherapy, a reversible significant increase in E–2 and SHBG was observed. Patients without antiproliferative treatment showed no significant changes in their comparable hormone levels; 15% of all normal T values were associated with elevated levels of SHBG and E–2. Although the aetiology of these hormonal changes remains unknown, they may be related to the clinical symptoms of hypogonadism displayed by 10 to 30% of patients undergoing treatment for testicular cancer.

About 10 to 30% of patients who are cured of testicular cancer complain of symptoms indicative of hypogonadism, such as decreased libido and reduced potency (Rieker *et al*, 1985; Levison, 1986; Schover *et al.*, 1986; Moynihan, 1987). In some of these patients low serum testosterone levels are found, but not all patients with low levels have these complaints and the symptoms may also occur in patients with normal levels. This variability indicates that the serum level of testosterone is not the sole determinant of clinical symptoms of hypogonadism in these patients.

Pyschological factors play an important role when reasons for sexual problems are investigated. On the other hand, hormonal disturbances other than low serum testosterone levels may cause a relative androgen insufficiency and thus be related to the development of symptoms of hypogonadism in testicular cancer patients. The working hypothesis was that alterations to the ratio between oestrogens and testosterone and variations in sex hormone binding globulin may occur after treatment for testicular cancer. The present study was designed to test this hypothesis by studying the serum levels of testosterone, oestradiol and SHBG in patients with testicular cancer before and after treatment.

Patients and Methods

The series comprised 84 patients with newly diagnosed testicular cancer referred to the Norwegian Radium Hospital between 1986 and 1987 (Table 1). All had undergone unilateral orchiectomy 1 to 3 weeks before admission and were staged according to the Royal Marsden classification system (Peckham *et al.*, 1979). Histology and stage determined the treatment in individual patients.

Details of the treatment policy have been recorded elsewhere (Fosså *et al.*, 1988). In principle, patients with metastatic non-seminoma and patients with advanced seminoma were given 3 or 4 cycles of cisplatin-based chemotherapy with or without surgery (*Group 1*: 27 patients). Patients with early seminoma received abdominal radiotherapy (30 Gy) (*Group 2*: 32 patients). Non-seminoma patients without metastases either underwent retroperitoneal surgery (15 patients) or

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Table 1 Details of Patients

	Group 1 (Chemotherapy)	*Group 2 (Radiotherapy)*	*Group 3 (No antiproliferative treatment)*	*Total*
Number	27	32	25	84
Age (years)	25* (17–53)†	31 (20–51)	27 (17—47)	28 (17–53)
Seminoma	1	32	0	33
Non-seminoma	26	0	25	51
Stage 1	3	31	25	59
Stage 2	19	1		20
Stage 4	5			5
Total dose of cisplatin (mg)	755 (400–800)			755 (400–800)
Midplane dose (Gy)		36 (36–40)		36 (36–40)
RLND‡	25		15	40

* Median.
† Range
‡ Retroperitoneal lymph node dissection.

were included in a surveillance protocol and received no treatment after orchiectomy (10 patients). Since no statistical differences were found between the serum hormone levels in these 2 subgroups, these patients were subsequently included in a "no antiproliferative treatment" group (*Group 3*: 25 patients). The duration of treatment (after orchiectomy) was 10 to 15 weeks for Group 1, 3 weeks for Group 2 and 0 to 2 weeks for Group 3. All patients were without evidence of disease during the follow-up period. Those in Group 2 had an increased median age compared with the other 2 groups ($P < 0.01$).

The serum levels of T, E–2 and SHBG were determined at the start of treatment, and 4 to 6 months and 12 to 15 months after discontinuation of all therapy. In addition, luteinising hormone (LH) and follicle stimulating hormone (FSH) were determined. Since changes in the levels of these hormones before and after treatment have been reported previously (Fosså *et al.*, 1985, 1986), they were not considered in the present investigation.

The serum levels of T, E–2 and SHBG were measured using the following commercially available kits: RSL ^{125}I Testosterone RIA (Biomedicals Inc., Carson, USA), ^{125}I Estradive RIA (Baxter Dade AG, Düdingen, Switzerland) and ^{125}I SHBG IRMA (Farmos Diagnostica, Turku, Finland). Normal serum ranges in our laboratory were as follows: T: 12–40 nmol/l; E–2: 0.04–0.11 nmol/l; SHBG: 10–40 nmol/l. The T × 100/SHBG ratio was calculated and used as an indicator for the level of free testosterone (Cunningham *et al.*, 1983) but no normal range had been established for this parameter.

Statistics

A PC-based software program "Medlog" was used for statistical analysis (median, ranges, Wilcoxon test). For changes in the serum hormone levels $P \leq 0.05$ was regarded as statistically significant.

Results

All patients (Table 2)

The median values for testosterone remained within the normal range throughout the observation period for all patients and for the different groups without significant changes. There was a transient but significant increase in E-2 and SBHG 4 to 6 months after discontinuation of treatment and a simultaneous decrease in the T × 100/SHBG ratio; 18% of all E-2 levels and 13% of all SHBG values were above the normal range (data not shown). Elevated values of E-2 and SHBG were observed only in patients with testosterone levels within the normal range.

Chemotherapy group (Table 3)

Four to 6 months after chemotherapy there was a reversible but significant increase in E-2 and SHBG with a comparable reduction in the T × 100/SHBG ratio. Twelve to 15 months after chemotherapy this ratio was still almost significantly decreased compared with the pre-treatment situation (*P* 0.02).

Table 2 Results in All Patients

	Time of analysis		
	Before treatment	*4–6 months after treatment*	*12–15 months after treatment*
Testosterone (T) (nmol/1)			
Median	19.9	20 1	18.5
Range	1.8–34 7	7.7–34.8	7.8–34 9
< normal	8/84*	8/82	5/77
Oestradiol (E-2) (nmol/1)			
Median	0.04	0 10‡	0.08
Range	0.04–0.35	0.05–0.27	0 5–0.15
> normal	17/84†	21/80	6/62
SHBG (nmol/1)			
Median	25.0	33.0‡	29.0
Range	8–98	10.0–72.0	8–55
> normal	5/84†	20/82	9/77
T × 100/SHBG			
Median	80	58‡	71
Range	7–261	25–200	22–265

*Number of patients with values below the normal range/number of evaluated patients

†Number of patients with values above the normal range/number of evaluated patients.

‡Significant changes compared with the pre-treatment situation.

Radiotherapy group (Table 4)

SHBG was significantly raised before treatment in this group compared with the other 2 groups, together with lower levels of free testosterone. On the other hand, the treatment-induced changes in E-2, SHBG and the T × 100/SHBG ratio were less pronounced in this group, reaching significance only for SHBG measured 4 to 6 months after radiotherapy.

Table 3 Chemotherapy Group

	Time of analysis		
	Before treatment	*4–6 months after treatment*	*12–15 months after treatment*
Testosterone (T) (nmol/1)			
Median	23.8	21.2	19.5
Range	7.4–34 7	8.7–33.9	10 0–34.7
< normal	3/27*	1/27	1/25
Oestradiol (E-2) (nmol/1)			
Median	0.08	0.11‡	0 08
Range	0.04–0.35	0.07–0.21	0.06–0 14
> normal	7/27†	10/26	4/23
SHBG (nmol/1)			
Median	25.0	35.0‡	30
Range	9.0–98	14.0–72.0	(114.0–42.0)
> normal	1/27	9/27	1/25
T × 100/SHBG			
Median	96	64‡	73
Range	24–210	30–129	37–223

*, †, ‡ See footnotes, Table 2.

Table 4 Radiotherapy Group

	Time of analysis		
	Before treatment	*4–6 months after treatment*	*12–15 months after treatment*
Testosterone (T) (nmol/1)			
Median	18.7	19.4	16.10
Range	9.4–34.7	7 7–34 8	7 8–34 9
< normal	3/32	3/31	3/29
Oestradiol (E-2) (nmol/l)			
Median	0.08	0.1	0.08
Range	0 06–0.13	0.06–0.27	0 65–0 10
> normal	5/32	6/31	0/20
SHBG (nmol/l)			
Median	31.5	34‡	30.0
Range	17.0–44.0	24–66	18.0–55.0
> normal	1/32	7/31	3/29
T × 100/SHBG			
Median	65	56	59
Range	26–123	25–102	22–135

‡See footnote, Table 2.

No antiproliferative treatment (Table 5)

No significant changes in serum hormone levels were found in this group. However, in these patients there was also a tendency to a transient increase in SHBG at 4 to 6 months, together with a reduction in the T × 100/SHBG ratio.

Discussion

This study confirms previous observations that about 10% of all testicular cancer patients have T levels below the normal range after unilateral orchiectomy and before further treatment (Berthelsen, 1984; Fosså *et al.* 1984). Increased E-2 levels were found in 20%. Although the serum testosterone levels subsequently increased to normal in some of these patients, a subnormal T level after orchiectomy and before further treatment probably reflected a slight hypogonadism. In the majority of patients the testosterone levels remained normal during the observation period, although in the lower part of the normal range, as described previously (Berthelsen, 1984; Fosså *et al.*, 1985, 1986). According to Leitner *et al.* (1986), however,

Table 5 No Cytostatic Treatment Group

	Time of analysis		
	Before treatment	*4–6 months after treatment*	*12–15 months after treatment*
Testosterone (T) (nmol/l)			
Median	19 5	20 3	18 7
Range	1.8–28.9	9.1–29 8	11 4–34 6
>normal	2/25*	4/24	1/23
Oestradiol (E–2) (nmol/l)			
Median	0.09	0.08	0.08
Range	0 04–0 16	0 05–0 14	0.05–0 15
>normal	5/25†	5/23	2/19
SHBG (nmol/l)			
Median	21.0	30.0	26.0
Range	8.0–53 0	10.0–55.0	8 0–46.0
>normal	3/25†	4/24	5/23
T × 100/SHBG			
Median	89	60	81
Range	7–261	34–200	34–265

*, † See footnotes, Table 2.

Leydig cell function and thus T production may be slightly reduced by systemic chemotherapy.

The most significant changes were the increase in E-2 and SHBG 4 to 6 months after chemotherapy and the increase in SHBG 4 to 6 months after radiotherapy. The exact cause of the increased E-2 levels is unclear. Disturbed Leydig cell function (Weinstein *et al.*, 1974) or increased production of E-2 by Sertoli cells (McFadyen *et al.*, 1980) have been proposed as probable reasons, the latter possibly due to previously demonstrated increases in serum gonadotrophins (Fosså *et al.*, 1985, 1986). Increased E-2 levels, together with relatively low T levels, have been demonstrated in testicular cancer patients as a reason for reversible gynaecomastia during the first year after treatment (Saeter *et al.*, 1987).

The increase in SHBG led to a transient reduction in the levels of free testosterone. Although the decrease in the T × 100/SHBG ratio was most pronounced after chemotherapy, the lowest absolute median values were measured in Group 2, which contained the "older" seminoma patients. Low free testosterone is thus most often found in this group. This may explain the observation by Schover *et al.* (1986) of frequent and age-related libido and potency disturbances in irradiated seminoma patients.

The aetiology of the changes in SHBG remains unknown. The use of chemotherapy or radiotherapy appears, however, to be related to these fluctuations, since significant changes were observed only in Groups 1 and 2. Such treatment may disturb the Leydig cell function of the remaining testis, at least transiently, causing an imbalance between oestrogen and testosterone production. This may result in increased serum E-2 levels which are often associated with elevated SHBG levels (Carlstrøm *et al.*, 1985). In addition, systemic chemotherapy and, to a lesser degree, radiotherapy to the upper abdomen may directly alter the hepatic production of SHBG.

From a clinical point of view it is important to bear in mind that 15 to 20% of testicular cancer patients with normal serum testosterone levels may display elevated serum E-2 and SHBG values and thus have decreased levels of free testosterone and an unfavourable oestrogen/testosterone balance. It is possible that the hormonal disturbances may be at least partly responsible for the disturbances in libido and potency sometimes encountered by patients treated for testicular cancer. When the present study was designed, measurement of serum hormone levels was the principal aim, and the patients' routine clinical records did not contain sufficient information to relate the individual serum levels with the patients' sex life. This will be the subject of further investigation.

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The Authors

Sophie D. Fosså, MD, PhD, Medical Oncologist and Radiotherapist; Consultant, Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital.

E Haug, MD, PhD, Specialist in Clinical Biochemistry, Consultant, Hormone Laboratory, Aker Hospital

Requests for reprints to: Sophie D Fosså, Department of Medical Oncology and Radiotherapy, Norwegian Radium Hospital, N-310 Oslo 3, Norway.

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Surgical Approach to the Retrocrural Lymph Nodes

W. HOELTL and S. AHARINEJAD

Department of Urology, Rudolfstiftung Hospital, and First Department of Anatomy, University of Vienna, Vienna, Austria

Summary—Removal of retrocrural lymph nodes requires an approach other than the infradiaphragmatic retroperitoneal access generally used in the surgical management of testicular tumours. The transperitoneal route given access, at best, to the origin of the superior mesenteric artery, but advanced testicular tumours occasionally require retrocrural node dissection. We describe a useful surgical approach to these nodes and the underlying anatomy.

As the management of advanced testicular neoplasms has improved, the need to remove clinically detectable residual disease persisting after chemotherapy has increased. Residual disease usually consists of mature teratoma tissue which failed to respond to chemotherapy. Mature teratomas are known to have a slow but definite progressive growth potential (growing teratoma syndrome) (Merrin *et al.*, 1975; Logothetis *et al.*, 1982) and a tendency towards later malignant degeneration, the extent of which is still poorly understood (Mostofi, personal communication). Thus their surgical removal is inevitable.

In cadaver dissection studies the anatomy was reviewed to establish the best approach to the retrocrural lymph nodes associated with minimal surgical trauma to the vessels and nerves of the diaphragm and the adrenal gland.

Materials and Methods

Anatomy

Preservation of the vessels and nerves during diaphragmatic incision requires a full understanding of the blood supply to the diaphragm. The diaphragm is supplied by 4 arteries:

(1) The pericardiacophrenic artery which accompanies the phrenic nerve towards caudal.
(2) The musculophrenic artery which, like (1) originates from the internal thoracic artery.
(3) The superior phrenic arteries from the thoracic aorta.
(4) The (abdominal) phrenic arteries, *i.e.* the first branches given off by the abdominal aorta after passing through the aortic hiatus of the diaphragm.

In planning surgery it is important to know that the lumbar part of the diaphragm will not suffer any perfusion deficits if the left (abdominal) phrenic artery is cut. This artery arises from the aorta just above the coeliac trunk. It is the first branch given off by the abdominal aorta and it courses posteriorly and superiorly along the crura of the diaphragm. During its course upwards the left phrenic artery passes behind the oesophagus and supplies the lumbar part of the diaphragm on its abdominal side.

Surgical technique

Cadaver studies were done initially in order to obtain the best possible exposure of the operative field by the surgical approach chosen. Experiments were also made with an approach from the right side. This proved to be more difficult, however, both because of the liver and because access to the left para-aortic retrocrural lymph nodes is impeded by the coeliac trunk, which is extremely short and drastically reduces manoeuvrability in the operative field.

Patients are placed in a 30° right lateral position (left side up). A left thoraco-abdominal incision is made. Beginning at the level of the seventh intercostal space in the anterior axillary line, it is

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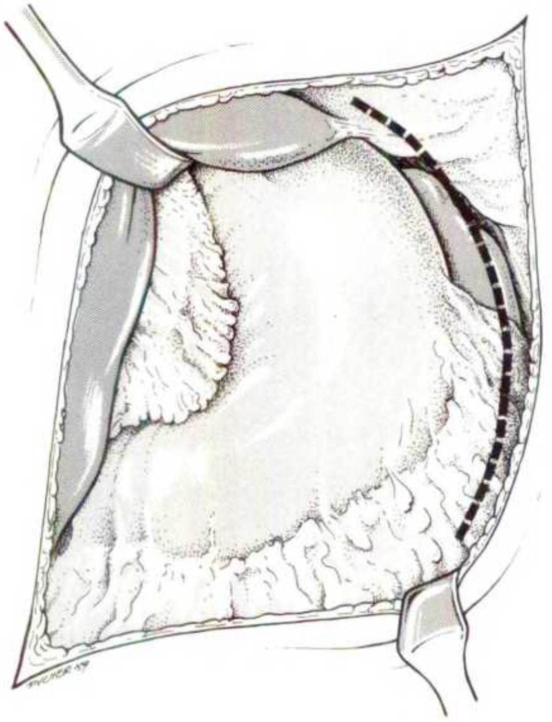

Fig. 1

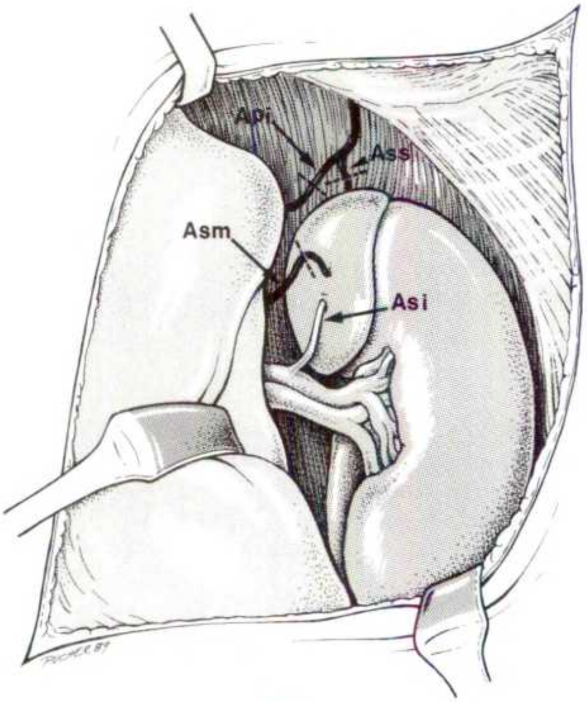

Fig. 2

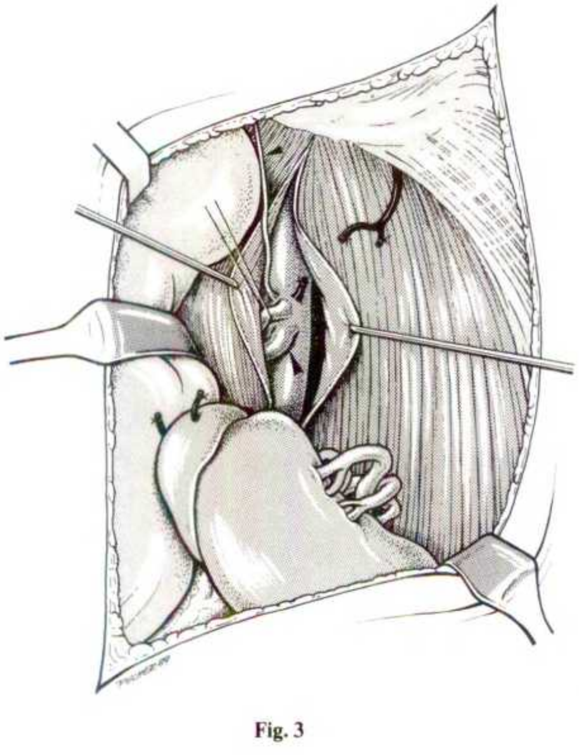

Fig. 3

Fig. 1 Left thoraco-abdominal incision, peritoneum opened. Interrupted line indicates incision in parietal peritoneum. **Fig. 2** Asi = inferior suprarenal artery. Asm = medial suprarenal artery. Api = inferior phrenic artery. Ass = superior suprarenal artery. **Fig. 3** Incision in the crus of the diaphragm. Large arrowhead marks superior mesenteric artery; coeliac trunk taped. Small arrowhead marks right inferior phrenic artery; left inferior phrenic artery cut.

continued pararectally to the level of the umbilicus. After splitting the ribs the diaphragm is incised as far laterally as possible to avoid injuring the left phrenic nerve, which enters the diaphragm at the level of the cardiac apex on the anterior aspect of the pericardium (Merendino, 1964). On entering the peritoneal cavity the parietal peritoneum is incised lateral to the colon; the incision should curve from about the mid-portion of the descending colon to the oesophageal aperture skirting the spleen laterally and superiorly (Fig. 1) so that the left colonic flexure together with the spleen and the pancreatic tail can be pulled medially and downwards. This exposes the upper pole of the kidney and the left adrenal (Mattox *et al.*, 1975). The superior and medial suprarenal arteries are ligated and cut so that the adrenal can be pushed downwards together with the upper pole of the kidney.

The inferior suprarenal artery, which originates from the left renal artery, must not be sacrificed because it will be the only vessel left to supply the adrenal gland. Above the origin of the left renal artery a DeBakey clamp is passed underneath the left crus of the diaphragm and advanced into the aortic hiatus along the lateral wall of the aorta. This manoeuvre should be done with the utmost care lest the left phrenic artery be torn from the aorta at its origin just below the aortic hiatus and above the origin of the coeliac axis. The left phrenic artery is cut together with the left crus of the diaphragm and ligated (Fig. 2). The diaphragmatic incision should be extended upwards to the level of the oesophageal hiatus (Fig. 3). At this level the mediastinal pleura may be opened inadvertently, but minor defects of the mediastinal pleura need not be sutured since a chest drain will have to be left in place. This approach provides excellent exposure of both the left and the right retrocrural lymph nodes up to the lower part of the posterior mediastinum.

To get a better view of the right para-aortic nodes it is helpful to tape the coeliac trunk, particularly if massively enlarged nodes on the right side have to be removed. In this area great care should be taken to spare the lumbar arteries, as the artery of Adamkiewicz, which may originate at variable sites on their dorsal aspect (or from the aorta between T6 and L2), must not be injured because of the risk of producing a spinal lesion (Jellinger, 1967).

To avoid major bleeding from the azygos vein, which runs behind the right para-aortic retrocrural lymph node group, nodal dissection is best started at the upper end of the tumour. Adequate exposure of the azygos vein can only be obtained at this level so that it can be clamped and ligated in full view, if necessary. Once the involved lymph nodes have been removed, drainage of the retrocrural space is unnecessary because lymph leaking into the peritoneal cavity will be absorbed spontaneously, but the cut edges of the crus of the diaphragm should be meticulously adapted and closed with a continuous suture. This leaves sufficient space for intraperitoneal lymphatic drainage between the diaphragm and the aorta. The thoracic and abdominal cavities are closed as usual.

Patients

Of 126 patients with testicular tumours treated between 1977 and 1985, 3 were in need of retrocrural lymph node dissection. They presented with the growing teratoma syndrome, *i.e.* with mature teratoma tissue that had persisted after chemotherapy and continued to grow slowly but did not yet show any signs of malignant degeneration. The tumour mass was 10 cm or more in length and 5 to 7 cm in diameter in all 3 cases. The mature teratoma tissue was easily shelled out without major blood loss. There were no post-operative complications related to the approach to the diaphragm and postoperative recovery was uneventful.

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The Authors

W Hoeltl, MD, Senior Registrar in Urology
S Aharinejad, MD, Resident in Anatomy

Requests for reprints to W. Hoeltl, Department of Urology, Rudolfstiftung Vienna, Juchgasse 25, A-1030 Vienna, Austria

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Blunt Renal Trauma in Childhood. Features Indicating Severe Injury

D. M. QUINLAN and J. P. GEARHART

Division of Pediatric Urology, James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, USA

Summary—The clinical presentation of children with blunt renal trauma may differ from that of adults. The clinical features at presentation of 50 consecutive children (20 severe injuries, no pedicle injuries) admitted over a period of almost 8 years were reviewed to determine if there were clinical clues to major renal trauma in childhood. Gross haematuria and low haematocrit were the most helpful factors at the time of presentation and correlated well with severe renal injury. Hypotension was seen in 4 patients and only 1 had severe renal trauma. Suspicion of a major renal injury should be high when there is gross haematuria or a low haematocrit. In this study only 1 of 20 patients with major renal injury demonstrated clinical signs of shock. Unlike adults, hypotension does not appear to be a reliable indicator of the severity of renal injury in children and diagnostic evaluation should not be reserved only for those in shock.

Trauma is the main killer and cause of morbidity in children between the ages of 1 and 14 years (Mendez, 1977). The paediatric kidney is the most commonly injured organ in blunt abdominal trauma (Morse, 1975). In paediatric trauma, renal injuries come second only to head injuries in frequency (Seruca *et al.*, 1979) and compared with adults, children are much more likely to suffer a major renal injury from blunt abdominal trauma (Reid, 1973).

There has been little emphasis recently on the clinical presentation of children with major renal injuries. History and physical examination are the immediate tools available at the time of presentation and the main determinants of initial management and diagnostic procedures. The purpose of this study was to determine what features in a child's immediate clinical presentation might point to a severe renal injury and ensure prompt diagnostic evaluation.

Patients and Methods

A retrospective review was made of 50 consecutive children under the age of 15 years. All had been admitted to this hospital with a diagnosis of blunt renal trauma between January 1979 and September 1986; 42 children had an IVU and 13 had CT scans to diagnose their injuries. Four items were selected in the child's history and 4 in the physical examination as possible indicators of severe renal injury. History was examined for the child's age at presentation, sex, mechanism of injury and side of renal injury. In the child's physical examination attention was given to the abdominal findings, haematuria, associated injuries and blood loss; χ^2 analysis was used to determine statistical significance.

Results

Grade of Renal Injury

Grading was done according to the system of Sargent and Marquardt (1950) wherein Grade I is a contusion (Fig. 1A) or a small subcapsular haematoma, Grade II is a renal laceration (Fig. 1B) extending through the capsule, and Grade III is a fractured kidney (Fig. 1C). Of the 50 patients in this series, 20 had major renal injuries (40%), including 10 renal lacerations (Grade II) and 10 fractures (Grade III). There were 30 contusions (60%) and no pedicle injuries.

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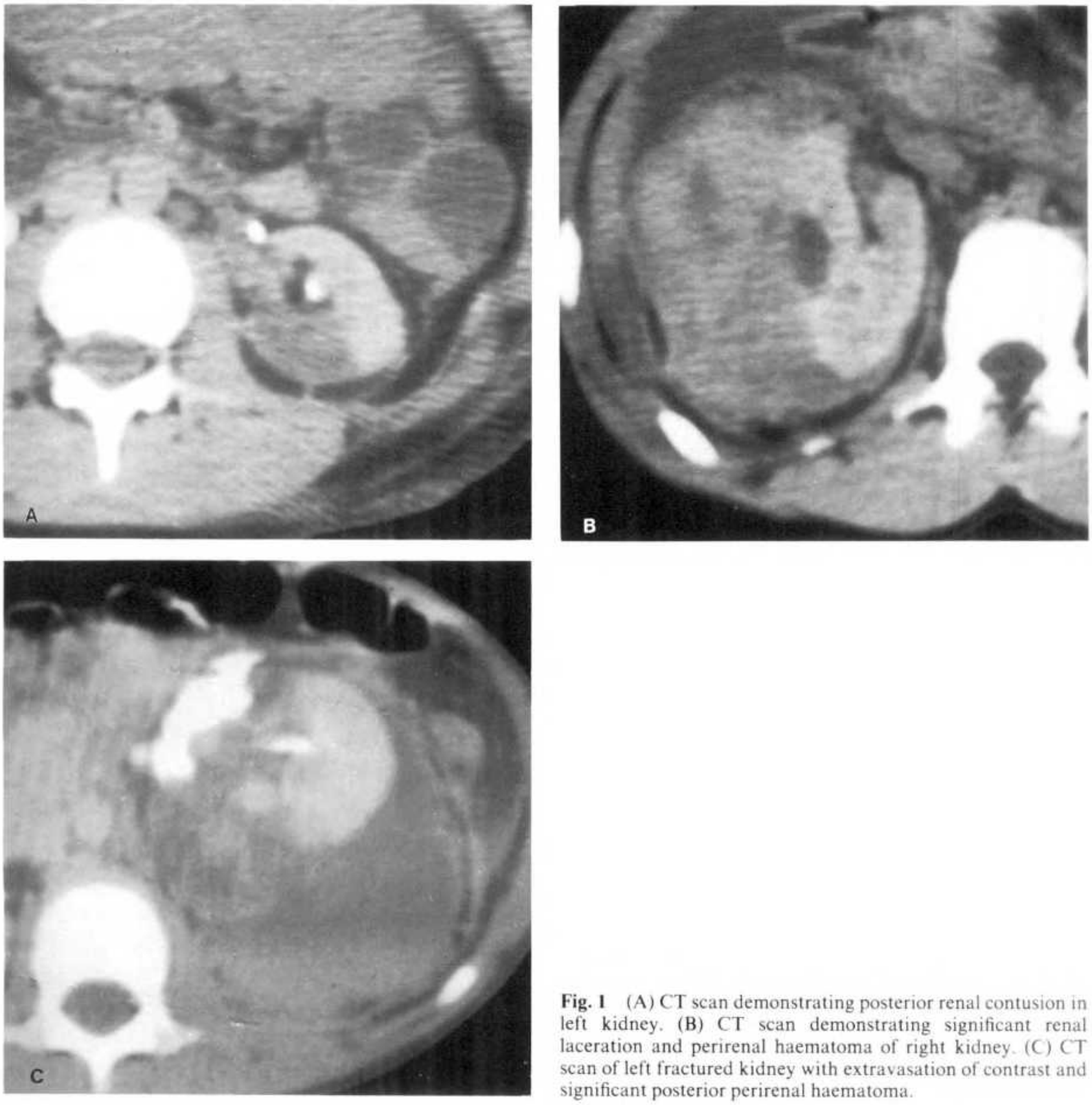

Fig. 1 (A) CT scan demonstrating posterior renal contusion in left kidney. (B) CT scan demonstrating significant renal laceration and perirenal haematoma of right kidney. (C) CT scan of left fractured kidney with extravasation of contrast and significant posterior perirenal haematoma.

Age

The children ranged in age from 1 to 14 years (average 8). Exactly half were in the 5 to 10 year age group, 7 were under 5 and 18 were 10 or older (Table 1). No particular age group appeared to be at greater risk of having a more severe injury.

Sex

Males outnumbered females by 4 to 1 (Table 1), but the females experienced more severe injuries than their male counterparts; 6 of 10 females had severe injuries (60%) compared with 14 of 40 males (35%). Girls also had a greater proportion of fractures (4, 40%) compared with boys (6, 15%). These differences did not achieve statistical significance.

Side of Injury

From the history of the accident, site of pain or tenderness, skin markings, other injuries (*i.e.* liver or spleen) and radiographic findings, the side of renal injury was determined in 45 patients (Table 1). In the remaining 5 patients (all contusions) there

Table 1 Details of Patients and Injuries

	Grade of injury			
	I	*II*	*III*	*Total*
Age (years)				
<5	4	2	1	7
5–10	14	4	7	25
⩾10	12	4	2	18
Sex				
Males	26	8	6	40
Females	4	2	4	10
Side of Injury				
Right	7	6	3	16
Left	18	4	7	29
Mechanism of Injury				
Fall	9	1	3	13
MVA (Ped)	16	7	3	26
MVA (Cycle)	1	1	1	3
MVA (Car)	4	1	2	7
Blows	0	0	1	1

MVA = motor vehicle accident. Ped = pedestrian.

was either too little information to lateralise or the information was contradictory. In 45 patients the left kidney (29 patients) was injured almost twice as often as the right (16 patients) ($P=0.05$). However, a serious renal injury was more likely on the right (9/16) than the left (11/29) but this did not achieve statistical significance ($P=0.24$).

Mechanism of Injury

Road traffic accidents (Table 1) accounted for 36 injuries (72%): 26 patients were pedestrians, 7 were passengers in cars and 3 were cyclists struck by motor vehicles. Thirteen children injured kidneys as a result of falls and 1 boy sustained a renal fracture after a direct blow to his kidney from a golf club. While 75% of all major renal injuries involved a motor vehicle and 42% of all motor vehicle accidents resulted in a serious renal injury, these figures merely reflect the percentage of total patients involved in road accidents (72%) and the percentage of total patients with severe renal injuries (40%).

Abdominal Findings

More than half of the 50 patients lacked abdominal signs suggestive of a renal injury (Table 2). Two patients had a frankly acute abdomen from splenic and hepatic injuries. The remaining 22 patients had tenderness and/or guarding in their hypochondria, their flanks or their renal angles posteriorly. Of these 22, half had contusions and half had serious injuries. Of patients with serious injuries, 55% had signs suggestive of a renal injury. Abdominal examination was unremarkable in 5 of 20 major renal injuries. There were no renal masses documented in 50 patients at the time of initial presentation.

Ileus was present in 16 patients; 70% of significant injuries (14 children) had an associated ileus; 28 of 30 patients with contusions (93%) had no ileus.

Associated injuries

Thirty-four patients had a total of 70 extrarenal injuries (Table 3). Head injuries predominated, with half of all patients presenting with some degree of head injury; 25% of children sustaining a severe renal injury (5 patients) had concomitant splenic or hepatic injury. Two of these required exploration involving a splenectomy in 1 and oversewing of a liver tear in the other. There were no known instances of bowel, mesenteric or pancreatic injuries. Thirteen children had femoral fractures result-

Table 2 Abdominal Findings according to Grade of Renal Injury

	Grade of injury			
	I	*II*	*III*	*Total*
Poorly localised	20	4	2	26
Upper Quadrant (UQ)	4	2	1	7
Costovertebral Angle (CVA)	2	1	2	5
UQ and CVA	2	1	2	5
Flank	3	1	1	5
Acute Abdomen	0	1	1	2
Renal Masses	0	0	0	0
Ileus	2	6	8	16
No Ileus	28	4	2	34

Table 3 Associated Injuries in 34 Patients according to Grade of Renal Injury

	Grade of injury			
	I	*II*	*III*	*Total*
Head	16	8	1	25
Femur	7	4	2	13
Face	5	3	1	9
Chest	2	2	1	5
Spleen	3	1	1	5
Liver	0	3	0	3
Pelvis	2	1	0	3
Clavicle	3	0	0	3
Forearm	1	0	1	2
Tibia	2	0	0	2

ing from road traffic accidents and 16 of these had serious renal injuries.

Sixteen patients had no other system injury; 11 of these had renal contusions but 5 had renal fractures. These 5 comprised 2 falls, 2 road accidents and 1 direct blow. A sixth child with a fracture as a result of a fall had a facial laceration as his only injury.

Haematuria

Of 21 children with gross Haematuria, 16 (76%) had significant renal injuries ($P=0.87\times10^{-5}$) (Table 4); 28 children had microscopic haematuria and only 3 of these (10%) resulted from a severe renal injury. Of 20 children with serious renal injuries, 16 (80%) had gross haematuria. There was only 1 patient without haematuria and this child had a cortical laceration.

Table 4 Haematuria in 50 Patients according to Grade of Injury

	Grade of injury			
Haematuria	*I*	*II*	*III*	*Total*
Gross	5	7	9	21
Microscopic	25	2	1	28
None	0	1	0	1

Table 5 Haematocrit (HCT) and Units of Blood Transfused according to Grade of Renal Injury

		Grade of injury			
		I	*II*	*III*	*Total*
HCT=	21	0	0	1	1
	22	0	1	1	2
	24	0	1	0	1
	26	1	2	0	3
	27	0	1	1	2
	28	1	1	0	2
	29	0	2	2	4
	30	0	0	3	3
	31	0	0	1	1
	32	3	0	0	3
	33	2	0	0	2
	34	2	1	1	4
	35	6	0	0	6
	36	6	0	0	6
	38	2	1	0	3
	39	2	0	0	2
	40	4	0	0	4
	44	1	0	0	1
Units=	1	1	5	2	8
	2	0	0	3	3
	5	0	0	1	1

Blood Loss

Twenty patients had heart rates >100. Of these, 5 had a major renal injury and 15 had minor injuries. Four children had blood pressure measurements with a systolic pressure <95 mm Hg: 3 of these children had minor injuries and 1 had a renal fracture.

When haematocrit measurements were studied, 18 patients had values under 32% and 16 (89%) of these had severe renal injuries ($P=0.12\times10^{-6}$). Nine of these 16 had associated injuries sufficient to explain their low haematocrit (*i.e.* chest, liver or splenic injuries or femoral fractures) but 7 did not. Twelve patients required transfusion of between 1 and 5 units of red blood cells and 11 of these had severe renal injuries; 8 of these had extrarenal injuries which on their own might have explained their blood loss, but 3 did not. Of 10 patients with renal fractures, 6 required transfusion. Two patients with major renal trauma and no associated injuries (both had renal fractures) required between 2 and 5 units of blood (Table 5).

Discussion

Children sustaining major blunt renal trauma require immediate diagnosis regardless of whether management is likely to be conservative or operative (Carlton, 1981). The purpose of this study was to determine what features in the child's immediate clinical presentation would increase suspicion of a severe renal injury.

Previous studies have looked at the incidence and severity of paediatric blunt renal injury by age group. There is disagreement on whether renal injury following blunt injury is more likely in the 5 to 10 year age group (Reid, 1973; Ahmed and Morris, 1982), the over 10 age group (Persky and Forsythe, 1962; Kuzmarov *et al.*, 1981; Cass, 1983) or neither (Emanuel *et al.*, 1977). In only 1 study was an association found between severity of renal injury and age (over 10) (Linke *et al.*, 1972). There is no evidence in the present series to suggest that the blunt renal injuries suffered in any particular paediatric age group were more severe.

Abdominal findings were disappointing in detecting major kidney trauma. Only 55% of children with significant renal injury had tenderness over their kidneys and almost half of all children with apparent renal tenderness had minor injuries. One quarter of those with severe injuries had an unremarkable abdominal examination. Earlier studies have shown that 12 to 58% of kidney injuries have a palpable mass (Mertz *et al.*, 1963; Fock *et al.*, 1966). Not one renal mass was documented on initial examination in our entire series. The development of ileus correlated better than other abdominal findings with severity of injury. However, an accurate diagnosis and a plan of management should be obtained before ileus becomes manifest. Suspicion of a major renal injury should not be allayed when abdominal findings are minimal or absent.

The number of associated injuries in this study was high, as in other series where road accidents predominated (Cass and Ireland, 1974; Cass, 1983). However, there were no specific organ system injuries which correlated well with severe renal trauma. Moreover, half of the patients with kidney fractures had no other injuries.

Boys outnumber girls with regard to blunt renal trauma (Persky and Forsythe, 1962; Seruca *et al.*, 1979). In the present study males outnumbered females by 4 to 1. Females, however, had almost twice the incidence of severe renal injuries and accounted for 4 of 10 renal fractures.

Previous studies disagree about whether renal injury is more common on the right (Mertz *et al.*, 1963), the left (Dowse and Kihn, 1963; Fock *et al.*, 1966; Javadpour *et al.*, 1973; Ahmed and Morris, 1982) or equal on both sides (Glen and Harvard, 1960; Scholl and Nation, 1963; Seruca *et al.*, 1979). Overall there appears to be a trend toward the left kidney. There have, however, been no reports suggesting that one kidney sustains more severe injuries than the other. Although the incidence of right renal injury was almost half that of the left, a severe injury was almost twice as likely on the right. The left kidney is more protected by the rib cage and the right would seem more at risk. However, the anatomical relations and attachments of the right and left kidneys are very different. Not only does the left kidney have fewer bare areas than the right, but peritoneal reflections over the left kidney form 2 ligamentous attachments not found on the right. These are the splenorenal ligament and the phrenicocolic ligament and may explain the limited renal movement seen on the left compared with the right (Preminger *et al.*, 1987). Given the more abundant rib cage posteriorly and the diminished movement afforded by its ligamentous attachments, the left kidney may be more vulnerable to crush injury from blunt abdominal trauma, resulting in a higher number of less significant injuries. The position, more mobile nature and larger bare area of the right kidney may afford it some escape in crush injuries of a minor nature but offer little protection from overwhelming blunt force and may result in a more serious grade of renal injury.

Haematuria is the cardinal sign of renal injury (Miller *et al.*, 1966). With the exception of renal pedicle injuries (where 50% may have no haematuria), the more severe degrees of haematuria parallel the more severe degrees of renal injury (Cass, 1983). Only 10% of our children had gross haematuria attributable to a minor injury. Conversely, only 10% had microscopic haematuria attributable to a major injury. The presence and type of haematuria is the most helpful clinical sign available to the clinician at the time of the child's initial presentation with a major renal injury. Gross haematuria is a significant finding and should point to a major renal injury. However, the absence of blood in the urine (as in pedicle injuries), or the presence of microscopic haematuria only, does not exclude severe kidney trauma.

Significant blood loss is a time honoured sign of major injury, regardless of the source. Renal deaths reported in the paediatric blunt trauma population are directly related to blood loss (Cass and Ireland, 1974). Part of the controversy regarding conservative versus surgical management, and much of the emphasis on rapid diagnosis of renal injuries, centres around ensuring that the patient will not succumb in the initial period to blood loss. Children with major renal injuries lose blood. Visibly, they may have significant bleeding directly into the collecting system which is seen as gross haematuria. Invisibly, there may be cortical bleeding resulting in perirenal haematomas and not clinically detectable. Haematocrit determinations are more helpful than pulse and blood pressure recordings in assessing this blood loss (Jevitch and Montero, 1969).

Nicolaisen *et al.* (1985), in a study of adult renal trauma, questioned the necessity of performing diagnostic studies on patients in the absence of clinical shock, the rationale being that the detection rate for major renal injury is very low. Children are able to maintain a normal blood pressure despite significant renal blood loss (Jevitch and Montero, 1969). In this study only 1 of 20 patients with major renal injury demonstrated clinical signs of shock. Unlike adults, hypotension does not appear to be a reliable indicator of the severity of renal injury in the childhood population. Any child with blood loss that cannot be attributed to other injuries should be suspected of having a major renal injury.

The ultimate goals in the management of a child with blunt renal trauma are to prevent mortality, reduce immediate and long-term morbidity and preserve as much functioning renal parenchyma as possible. Achieving these goals involves making the diagnosis of renal injury as quickly as possible, invoking the appropriate imaging technique(s) to classify the injury accurately and having the judgement to recognise injuries that require immediate operative intervention and those that can be safely managed conservatively.

A timely diagnosis of severe blunt renal trauma will only be made by a clinician who considers this possibility and recognises its clinical features. History is helpful only in so far as right-sided injuries may be associated with a more severe grade of renal injury. Abdominal examination is not a reliable aid in either detecting or excluding major renal trauma. Gross haematuria is the single most important clinical clue and its presence should dictate active exclusion of a major renal injury. In addition, any child with bleeding not explained by associated injuries should be suspected of having a significant renal injury. Haematocrit is better than the clinical measurement of blood pressure and pulse in assessing renal blood loss. Hypotension is unreliable in determining which child has suffered a severe renal injury. A policy of performing radiological studies only on patients with shock should not be applied to the paediatric population.

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The Authors

D M Quinlan, FRCSI, Chief Resident, Assistant Chief of Service and Instructor in Urology.

J. P. Gearhart, MD, FACS, FAAP, Consultant Paediatric Urologist, Assistant Professor, Department of Urology, and Assistant director, Division of Paediatric Urology.

Request for reprints to: D. M. Quinlan, Department of Urology, St Vincent's Hospital, Dublin 4, Ireland.

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Treatment of Infants with Neurogenic Bladder Dysfunction using Anticholinergic Drugs and Intermittent Catheterisation

L. S. BASKIN, B. A. KOGAN and F. BENARD

Department of Urology, University of California School of Medicine, San Francisco, USA

Summary—The use of anticholinergic drugs in infants with neurogenic dysfunction has not been well documented. In this study, 35 neonates at risk of upper urinary tract damage from neurogenic dysfunction were treated from infancy with anticholinergics, in combination with clean intermittent catheterisation. None of the patients showed upper urinary tract deterioration with follow-up ranging from 6 to 72 months, although 2 required vesicostomy—1 due to difficulty with catheterisation and 1 due to possible anticholinergic side effects. Only 2 (6%) have had clinical pyelonephritis. Twenty-five (76%) are virtually dry between catheterisation. We conclude that anticholinergics are safe and effective, even in the neonatal period, when used in combination with clean intermittent catheterisation for the treatment of neonates with neurogenic bladder dysfunction.

Urodynamic evaluation of infants with myelomeningocele and neurogenic bladder dysfunction can predict those at highest risk of upper urinary tract deterioration (Bauer *et al.*, 1984). They can then be effectively managed with prophylactic clean intermittent catheterisation (Geraniotis *et al.*, 1988). In myelomeningocele patients with small capacity bladders and hypertonicity, anticholinergic drugs have proved effective (Bauer, 1989) and, in combination with clean intermittent catheterisation, represent standard therapy for children and adults with dysfunctional bladders. However, their use in the neonatal period has not been well documented. In this study we examine the hypothesis that anticholinergic drugs, in combination with clean intermittent catheterisation, can be safe and effective therapy for newborns with myelomeningocele and neurogenic bladder dysfunction.

Patients and Methods

Between 1983 and 1988, 48 neonates (age 1–30 days) with myelomeningocele were evaluated by urine analysis and culture, renal and bladder ultrasonography, cystography and urodynamics (Table). Based on initial urodynamic evaluation at 9 to 30 days of age, the infants were separated into groups: 13 (27%) were found to have an extremely

Table Characteristics of Neonates with Myelomeningocele and Neurogenic Bladder Dysfunction

	Treatment group (bladder spasticity or hypertonicity and significant sphincter dyssynergia) (n=35)		*Observation group (extremely lax sphincter) (n=13)*	
		(%)		(%)
Boys	11	(31)	8	(62)
Girls	24	(69)	5	(38)
Level of defect				
Thoracic	1	(3)	0	
Thoracic/lumbar	2	(6)	0	
Lumbar	17	(48)	7	(54)
Lumbar/sacral	13	(38)	5	(38)
Sacral	2	(6)	1	(8)
Vesicoureteric reflux				
Bilateral	3	(9)	1	(8)
Left	6	(16)	2	(15)
Right	3	(9)	1	(8)
No reflux	23	(66)	9	(69)

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flaccid external sphincter and were initially managed by close observation; 30 (62%) had a spastic or hypertonic bladder with significant bladder-sphincter dyssynergia; 5 (10%) were initially diagnosed as having a flaccid bladder and urinary retention owing to moderate sphincteric activity. All 5 ultimately developed a high pressure bladder (either spasticity or hypertonicity). The latter 35 patients form the basis of this study. They were managed with anticholinergics (oxybutynin, generally 0.1 mg/kg *tid*) and clean intermittent catheterisation, all beginning as neonates. None underwent an initial vesicostomy. All patients were followed up in the multidisciplinary Spinal Defects Clinic at the University of California, San Francisco. Upper urinary tracts were monitored by renal sonography. Routine interview, physical examination, urine analysis and urine culture were performed at quarterly visits.

Results

Follow-up for the observation group (8 boys, 5 girls) ranged from 20 to 60 months (mean ± SD, 44 ± 16 months). None developed a urinary tract infection or upper tract deterioration (based on normal or stable findings on renal sonography).

Follow-up in the 35 patients (11 boys, 24 girls) in the treatment group ranged from 6 to 72 months (mean ± SD, 39 ± 18 months). Two patients (6%) were withdrawn from the treatment group, 1 boy secondary to possible urethral trauma and 1 girl because of progressive hydronephrosis secondary to a failure to take or respond to oxybutynin. Both have done well with cutaneous vesicostomy. None of the 33 patients (94%) who have continued with anticholinergics and clean intermittent catheterisation has shown any deterioration of the upper urinary tract.

Ten patients (30%) have had no urinary infections; 21 (64%) have had at least 1 episode of "asymptomatic" bacteriuria, in many cases not treated, but 10 of these (29%) had increased wetting between catheterisations and were treated; 2 (6%) have had at least 1 episode of clinical pyelonephritis. In general, infections were associated with poor parental compliance. Twenty-five (76%) are virtually dry between catheterisations, with the remaining 8 having significant wetting. Only 2 demonstrated persistently elevated intravesical pressure. The others had stress incontinence owing to relatively decreased sphincteric activity.

Constipation was a common side effect, but was effectively managed with alterations in diet or bowel programme. In 1 case, anticholinergics were stopped secondary to "sedation" and 1 child disliked the taste and stopped temporarily. In children exposed to extreme summer heat, facial flushing was common and the dosage was adjusted (smaller daytime and larger evening dosages). In no instance did this result in discontinuation of the anticholinergics. A number of other symptoms were occasionally reported, including sedation, hyperactivity, fever diarrhoea and stuttering, but they were not consistently related to the oxybutynin, as a change in dosage or cessation and reinstatement had no uniform effect.

Discussion

The value of early urodynamic assessment in newborns with myelodysplasia is well recognised (McGuire *et al.*, 1981; Rickwood *et al.*, 1982; Bauer *et al.*, 1984; Mundy *et al.*, 1985). Based on initial testing, neonates can be divided into 3 categories: those with (1) an extremely flaccid external sphincter, (2) moderate sphincteric activity with a flaccid bladder, or (3) a high pressure bladder with significant bladder-sphincter dyssynergia. Infants who fall into this last category are at risk of subsequent urinary tract changes such as reflux and hydronephrosis. For example, Bauer *et al.* (1984) followed the natural history of 18 such neonates and observed upper urinary tract deterioration in 13 (72%). The prophylactic use of clean intermittent catheterisation in children and adults with myelomeningocele and neurogenic bladder dysfunction has been shown to prevent these detrimental urinary tract changes as well as the need for urinary diversion. (Geraniotis *et al.*, 1988; Bauer, 1989; Joseph *et al.*, 1989). In the neonate, however, the concomitant use of anticholinergic medication has not been addressed, particularly the safety of this therapy.

We have shown that the combination of anticholinergic drugs and clean intermittent catheterisation is both safe and effective in preventing urinary tract deterioration in neonates with myelomeningocele and neurogenic bladder dysfunction. In our experience with 35 such infants, only 2 (6%) required alternative therapy (vesicostomy). In the remaining 33 (94%), the upper tracts were preserved and in most cases (76%) urinary continence was maintained. Previously, it had been thought that the risks of urinary tract infection and urethral trauma might limit the effectiveness of a clean intermittent catheterisation programme in infants. However, in only 1 of our 11 male neonates was difficulty in catheterisation a factor resulting in a vesicostomy (this patient had multiple caregivers and also stopped anticholinergics due to sedation). No other patient experienced urethral trauma. Thus our study corroborates the results of others (Kass *et al.*, 1979) that clean intermittent catheterisation can be an effective form of therapy, even in neonates (Geraniotis *et al.*, 1988; Joseph *et al.*, 1989).

Because the major aetiology of the renal deterioration in these infants is the high intravesical pressure, one principle of management is to convert these bladders to a low pressure reservoir. Hence the use of anticholinergic agents in conjunction with intermittent catheterisation is theoretically important. The safe use of anticholinergic drugs, specifically oxybutynin, is documented in adults and children (Diokno and Lapides, 1972) but not in neonates. Anticholinergic medications work by blocking the action of acetylcholine at the postganglionic cholinergic receptors, thereby increasing bladder capacity by reducing the number of motor impulses reaching the detrusor muscle. Oxybutynin has both anticholinergic and direct antispasmodic actions on the urinary bladder (the latter by an unknown mechanism) as well as mild analgesic properties (Baigrie *et al.*, 1988). We found the chronic use of oxybutynin (generally 0.1 mg/kg *tid*) to be well tolerated in our combined programme of anticholinergic medication and clean intermittent catheterisation. Constipation, the most common side effect, was managed by diet, stool softeners and mechanical emptying. In myelodysplastic children, moderate constipation can be beneficial to faecal continence if regular emptying can be achieved.

In this series, all 5 patients who initially had moderate sphincteric activity with a flaccid bladder eventually developed a high pressure bladder. This finding is consistent with the concept of spinal shock bladder in the newborn and may be secondary to repair of the spinal defect or placement of a ventriculo-peritoneal shunt for hydrocephalus. Infants who initially present with a flaccid bladder should be followed closely in the first few weeks of life. If incontinence develops between catheterisation, urodynamic studies should be repeated. In all 5 of our patients, results showed bladder spasticity or hypertonicity. As a corollary, all patients with a history of myelomeningocele repair are at risk of spinal cord tethering. This can present as new urinary incontinence, symptomatic infection and stool soiling (Kaplan *et al.*, 1988). A change in clinical status during follow-up should warrant recharacterisation of bladder function.

In conclusion, spinal shock bladder is a real finding in neonates with myelomeningocele, and those with a flaccid bladder on initial evaluation in the first few weeks of life should be observed closely. In those infants with bladder spasticity or hypertonicity, anticholinergic medications are safe and effective and can be initiated in the neonatal period. In combination with clean intermittent catheterisation, therapeutic intervention in the neonate can prevent urinary tract deterioration.

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The Authors

L. S. Baskin, MD, Chief Resident in Urology.

B. A Kogan, MD, Associate Professor of Urology, Departments of Urology and Pediatrics; Chief, Pediatric Urology Service

F Bernard, MD, formerly Post-doctoral Research Fellow, Department of Urology. Now Assistant Professor, Hotel Dieu de Montreal Hospital, Montreal, Canada.

Requests for reprints to. B. A Kogan, Department of Urology, U-518, University of California, San Francisco, CA 94143-0738, USA

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Treatment with Desmopressin in Severe Nocturnal Enuresis in Childhood

R. A. JANKNEGT and A. J. SMANS

Departments of Urology, Groot Ziekengasthuis, 's-Hertogenbosch and Anna Ziekenhuis, Oss, The Netherlands

Summary—A series of 22 patients with severe nocturnal enuresis were treated with desmopressin in a randomised double-blind cross-over study. Treatment with 20 and 40 μg was highly effective compared with placebo. No difference in dry nights was found between the 2 dosages. Desmopressin proved to be a safe and effective treatment.

There have been many reports on the efficacy and safety of desmopressin (Minrin, Ferring AB, Malmö, Sweden) in the management of nocturnal enuresis (Klauber, 1989). Almost all studies concentrated on short-term treatment, *i.e.* 2 weeks of active treatment, with desmopressin administered intranasally by means of a rhinal catheter. A mean increase of 130% was reported in the number of dry nights per week, ranging from 85% (Terho and Kekomäki, 1984) to 188% (Birkasova *et al.*, 1978). Wille (1986) showed that desmopressin had a rapid action and its effect was consistent over a long period of time. In most of these studies a fixed dose of 20 μg was used but it has been suggested that 40 μg might be more effective (Birkasova *et al.*, 1978; Terho and Kekomäki, 1984).

Most previous investigations have described the effect of desmopressin compared with placebo or conditioning devices. The studies were of a relatively short duration, usually between 2 and 4 weeks, and the patients comprised a heterogeneous population, with a mixture of mild and severe forms of nocturnal enuresis. Only Ferrie *et al.* (1984) considered the merits of desmopressin in treating severe, life-long enuresis. Theirs was a double-blind, cross-over study and failed to find any statistical significance compared with placebo. However, a feature of this trial was that the dose of desmopressin used (20 μg) was suboptimal and 40 μg might have been more effective (Birkasova *et al.*, 1978; Terho and Kekomäki, 1984). To date, there have been no reports on the relative merits of decompression in a controlled study of patients with intractable enuresis using a dose of 40 μg. The purpose of the present study was to compare the efficacy and safety of 2 dose levels of desmopressin with placebo in the management of intractable primary nocturnal enuresis in children.

Patients and Methods

The series included 22 children (18 boys and 4 girls) with a mean age of 10 ± 3 years (range 6–16) and a history of severe, life-long, intractable enuresis. All had a maximum of 4 dry nights per week during a 4-week pre-treatment observation period. No patient had day-time urological symptoms or recognisable underlying pathology. They were randomly allocated to 1-month periods on 20 μg and 40 μg desmopressin, with a 1-month placebo period between the active periods.

During the 12-week study period, patients were asked to take the contents of 2 single-dose pipettes just before bed-time. For patients in the placebo group both pipettes contained placebo. For the 20 μg group 1 pipette contained placebo and the other 20 μg desmopressin. For the 40 μg group each pipette contained 20 μg desmopressin. Patients kept a diary of dry/wet nights. Body weight, blood pressure, haematological parameters, urine analysis and blood chemistry were checked regularly. Informed consent was given by the parents of the patients.

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Results

All 22 patients completed the 16-week treatment and observation period. In the past, they had undergone a total of 43 regimens to treat enuresis (Table 1), mainly imipramine. All were able to concentrate their urine to normal values after a standard water deprivation test before entering the study. Routine urine analysis was negative before inclusion.

The number of dry nights per week is shown in Table 2. During the observation period, records showed an average of 1.3 dry nights per week. Treatment with desmopressin doubled the number of dry nights compared with pre-treatment and placebo. Compared with pre-treatment values, the differences were statistically significant (ANOVA, $P<0.05$) during all periods except the placebo period. No differences between the 2 dose levels of desmopressin were seen (significance level of 5% and power of 80%). However, during both periods of active treatment the patients were significantly dryer than during the placebo period (ANOVA, $P<0.01$). No correlation was found between age or body weight and the results of treatment.

A significant increase in body weight was seen during the period of observation. No significant changes were seen in blood pressure, haematology or blood chemistry. Morning urinary osmolarity was not significantly different in the pre-treatment or treatment periods. The commonest adverse reactions were headache (3 patients, 8 episodes) and stomach pain (3 patients, 8 episodes). However, we found no significant difference between placebo and active treatment. No epistaxis was reported. One patient dropped out during the post-treatment observation period because of severe enuresis but was reinstated on 40 µg desmopressin.

Table 1 Details of Previous Treatment

Therapy	*No of courses*
Imipramine hydrochloride	22
Imipramine hydrochloride + propranthelıne bromide	1
Imipramine hydrochloride + oxyphenium bromide	2
Propranthelıne bromide	3
Oxyphenium bromide	2
Ephedrine	1
Desmopressin	2
Enuresis alarm	8
Acupuncture	1
Psychotherapy	1
Total	43

(More than 1 method was used in many patients)

Table 2 Number of Dry nights per Week before, during and after Treatment

	(Mean ± SD)
Before treatment	1.3 ± 1.3
Placebo	1.7 ± 1.8
20 µg desmopressin	3.6 ± 2.5
40 µg desmopressin	3.2 ± 2.2
After treatment	2.2 ± 1.8

Discussion

In this study, intranasal desmopressin increased the mean number of dry nights per week by 177% (20 µg) and 146% (40 µg). This is in agreement with previous findings. We were unable to show that the higher dose of desmopressin was more effective than the standard dose. This is in contrast to reports by Birkasova *et al.* (1978) and Post *et al.* (1983). The pipettes which we used gave precise doses, whereas the rhinal method is less precise and may cause variations in dosage (Grossman *et al.*, 1980). In addition, during the study by Post *et al.* (1983), patients receiving the higher dose had slightly fewer enuretic episodes before treatment than those on the lower dose. This may be a predisposing factor which influences the outcome of treatment.

When compared with placebo, desmopressin significantly decreased the number of enuretic episodes, but no significant difference was found between the 2 doses of desmopressin. As noted by others, the relapse rate was high and only 1 of our patients remained dry during follow-up.

This series included 9 and 10 non-responders (<25% improvement compared with pre-treatment) during the 20 µg and 40 µg periods respectively, but in view of the highly selected population this was not unexpected. Of these 19 patients only 8 failed to respond in both treatment arms; 2 of these increased their mean number of dry nights by approximately 1/week and 6 were completely wet throughout the study period. This corresponds to 27% non-responders of the patients with intractable enuresis and correlates well with findings in other studies. None of the patients had diurnal symptoms and they had not previously reacted favourably to anticholinergics, so that bladder instability was an unlikely cause. Insufficient absorption through the nasal mucosa due to faulty administration of the drug should be considered.

Post *et al.* (1983) indicated that older children responded more favourably to desmopressin than younger ones, as did those who had relatively few enuretic episodes before treatment. We found no correlation between age and treatment or between body weight and results. On the other hand, there was a significant correlation between pre-treatment enuretic episodes and the response to desmopressin. Patients with more dry nights before treatment responded better.

Questions are often raised about the risk of overdosage and resulting accumulation of fluid in the body, but there have been no reports of water retention or intoxication. The increase in body weight observed during the present study was unrelated to the type of treatment and was due to normal growth. Patient compliance was satisfactory. In contrast to the experience of Ferrie *et al.* (1984) and Dimson (1977), no epistaxis was reported or any problems with dosing. The pipettes seemed more satisfactory than the rhinal catheter.

We have been encouraged by the results of desmopressin treatment in this highly selected group of patients with intractable enuresis. The positive correlation between pre-treatment dry nights and response to desmopressin may be a useful predictor of response. Further studies on larger groups of children may help to evaluate this factor.

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The Authors

R A Janknegt, MD, PhD, formerly Urologist, Groot Ziekengasthuis Now Chairman, Department of Urology, Academic Hospital, Maastricht.

A J Smans, MD, Urologist, Groot Ziekengasthuis and Anna Ziekenhuis

Requests for reprints to· R. A. Janknegt, Department of Urology, Academic Hospital, St Annadal 1, NL-6214 PA Maastricht, The Netherlands

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Vasa Aplasia and Cystic Fibrosis

N. D. HEATON and J. P. PRYOR

Department of Urology, King's College Hospital, London

Summary—Bilateral vasa aplasia is considered an invariable finding in cystic fibrosis, but such patients are rarely seen in male infertility clinics. The improved survival beyond 20 years of age is likely to change this. In a clinical study of a group of male cystics the vasa were absent in 8 of 11 boys and epididymal abnormalities were palpable in the majority. The main cause of infertility appears to be mechanical obstruction. Whether the absence is due to a primary failure of mesonephric duct development or secondary to luminal obstruction and subsequent atrophy is not known.

It has been stated that bilateral congenital absence of the vas is an almost invariable finding in cystic fibrosis (Kaplan *et al.*, 1968; Valman and France, 1969) and yet such patients are rarely seen in male infertility clinics. The incidence of vasa aplasia in azoospermic men presenting with infertility in a personal series (J.P.P.) was 18% (Table 1). Until a recent presentation there had not been a single patient with cystic fibrosis and this seems to be representative of other studies from infertility clinics (Girgis *et al.*, 1969). Previous publications have reported the incidence of vasa aplasia in cystic fibrosis to range between 67 and 90% (Table 2).

In the past, few children with cystic fibrosis survived beyond childhood, but nowadays 50% of patients survive beyond the age of 20 years and the question of fertility is becoming a matter of increasing concern. The current absence of cystic fibrosis patients in infertility clinics may be the result of early counselling at specialist centres and the social isolation of many of the patients (Mearns, 1986).

Table 1 Incidence of Vasa Aplasia in 321 Azoospermic Men

Site of obstruction	*No.*	*(%)*
Intra-testicular	47	(16)
Epididymal	163	(51)
Bilateral vasa aplasia	58	(18)
Unilateral vasa aplasia	11	(3)
Vasal	39	(12)
Ejaculatory duct	3	(1)

Table 2 Incidence of Vasa Aplasia in Cystic Fibrosis

	No.	*(%)*
Kaplan *et al* (1968)	24/28	(86)
Landing *et al* (1969)	28/32	(88)
Valman *et al.* (1969)	1/10 (9 fibrous cords)	
Olson and Weaver (1969)	19/27 (sides)	(70)
Feigelson and Pecau (1986)	9/10	(90)

A 31-year-old man with infertility and cystic fibrosis was referred for consideration of sperm retrieval from the epididymis in association with *in vitro* fertilisation (Pryor *et al.*, 1984; Silber *et al.*, 1987). Although diagnosed at the age of 13 years and suffering from recurrent chest infections, he remained in good health. He had been married for 4 years and wished to have children. On examination he had normal testes; the superior pole of the right epididymis was present but the body and tail were absent. However, on the left, the epididymis and a 3-cm segment of vas were present.

The results of seminal fluid analysis are listed in Table 3 and confirm the findings of previous studies (Denning *et al.*, 1968; Feigelson and Pecau, 1986).

A study was undertaken to determine whether bilateral vasa aplasia was as common an occurrence in males with cystic fibrosis as previously reported.

Patients and Methods

Eleven boys known to have cystic fibrosis (age range 18 months–14 years, mean 7.4 years) under review at the Brompton Hospital were examined

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Table 3 Seminal Fluid Analysis in Vasa Aplasia Associated with Cystic Fibrosis

Low volume
Azoospermia
Acid pH
Fructose absent

with parental consent and the approval of the ethical committee. The diagnosis of cystic fibrosis was conclusive in all patients.

Results

It was possible to palpate the vasa in 2 boys aged 7 and 14 years; the vasa were impalpable in 8 boys and in a further patient the examination was inconclusive.

In all patients a variable part of the superior pole of the epididymis was palpable, but in the 2 boys with palpable vasa the epididymides appeared to be normal. The testes were normal in all patients except for one 7-year-old with an atrophic right testis, a lax left hydrocele and bilateral vasa aplasia. A further patient had undergone an inguinal hernia repair, giving an incidence of 18% for inguinal canal and scrotal abnormalities. There appeared to be no association between the clinical manifestations, severity of disease and the presence or absence of the vas deferens.

Discussion

Cystic fibrosis is an autosomal recessive single gene defect that is present in a homozygote state in approximately 1 of every 2500 live births in the United Kingdom. A defect in membrane transport of water and electrolytes is suspected to be the basic abnormality responsible for the clinical manifestations of the disease. The main abnormalities occur in the lungs, gastro-intestinal tract, liver and pancreas, with added metabolic complications. These disorders arise primarily through abnormal mucus production (Landau, 1987).

About 1 in 20 individuals in the United Kingdom are thought to be heterozygotes carrying the cystic fibrosis gene (Kuzemko, 1986). If this estimate is correct, there are approximately 2,000,000 heterozygote carriers in the United Kingdom.

The incidence of vasa aplasia in adult cystics is likely to be similar to that in the group of patients examined (82% vasa aplasia), but azoospermia appears to be present in almost 100% of patients (Denning *et al.*, 1968). Mechanical obstruction appears to be the main course of infertility (Kaplan *et al.*, 1968) but secretory disorders, abnormalities of cilial or spermatozoal motility and spermatozoal maturation may be contributory in the small number of patients with patent vasa. Active spermatogenesis was described by Denning *et al.* (1968) and Kaplan *et al.* (1968) in the testes of patients with cystic fibrosis, although the number of spermatozoa was reduced and many were immature or abnormal in appearance. Previous studies quote an incidence for inguinal hernia ranging from 6 to 15%.

The vas deferens develop from the mesonephric duct and failure of early duct development (in the absence of cystic fibrosis) is associated with a high incidence of ipsilateral renal anomalies, including absence. Bilateral early mesonephric duct failure is incompatible with life. Late failure of mesonephric duct development at the 60-mm fetus stage results in vasa aplasia with normal renal tract development and is often bilateral. It is not known whether vasa aplasia in cystic fibrosis is due to primary failure of late mesonephric duct development or if it is secondary to inspissated mucus causing luminal obstruction with subsequent atrophy (Kaplan *et al.*, 1968; Gracey *et al.*, 1969). If it is a developmental failure, other structures which have a mesonephric duct origin should also be absent. These include the body of the epididymis, seminal vesicle, ampulla and ejaculatory duct. The globus major, including the efferent and epididymal ducts, develop with the testis from the genital ridge and might be expected to develop normally. Landing *et al.* (1969), in a pathological study of the genitalia of 32 cystic males, found absent vasa in 32 and the epididymides were invariably absent. The efferent ducts and globus major were present and often enlarged but the epididymal duct was usually hypoplastic or absent. Kaplan *et al.* (1968) described rudimentary or absent epididymides in 5 of 10 cystic patients. Oppenheimer and Easterley (1969) described microscopically normal vasa in 8 of 14 patients and normal epididymides in 13 of 20 patients. Although the testes appear to develop normally, the superior pole of the epididymis, efferent and epididymal ducts may be absent or hypoplastic in up to 50% of patients with cystic fibrosis (Kaplan *et al.*, 1968; Landing *et al.*, 1969; Olson and Weaver, 1969; Valman and France, 1969). Fertile male cystic patients have occasionally been described and in a postal survey 8 of 117 were believed to have fathered children (Taussig *et al.*, 1972).

There are other syndromes with associations between male infertility and pulmonary disease which have to be excluded. Immotile cilia syndrome is an inherited disorder characterised by chronic sino-pulmonary infection and infertility due to immobile spermatozoa (Afzelius *et al.*, 1975). Approximately 50% of patients have an associated *situs inversus*, better known as Kartagener's syndrome. Ultrastructural studies have revealed cilial abnormalities (Eliasson *et al.*, 1977). A third group of patients have bronchitis and bronchiectasis associated with obstructive azoospermia or Young's syndrome (Young, 1970). The vasa are present but sperm transport fails at the junction of the upper and middle thirds of the epididymis; the ultrastructure of the cilia appear to be normal (Hendry *et al.*, 1978).

The improved life expectancy of patients with cystic fibrosis raises difficult questions regarding the wish of male patients to father children. The presence in some cystic patients of epididymal ducts and active spermatogenesis has raised the possibility of spermatozoal retrieval. In 1984 a single pregnancy was reported after operative sperm retrieval from a patient with obstructive azoospermia, but this early success has proved difficult to repeat (Pryor *et al.*, 1984). In 1988, Patrizio *et al.* described a successful conception following microsurgical epididymal sperm aspiration combined with *in vitro* fertilisation and tubal embryo transfer for infertility secondary to bilateral vasa aplasia. *In vitro* fertilisation has been thought unlikely to succeed because of spermatozoal immaturity in the abnormal epididymis. Patrizio *et al.* (1988) reported that in men with vasa aplasia the most motile spermatozoa were found in the proximal part of the caput epididymis, near the vasa efferentia. Contrary to previous investigators, they thought that spermatozoa which had not passed through the epididymis were capable of fertilising oocytes *in vitro*. They described 3 successful pregnancies following 10 tubal transfers.

The ethical problems of treating infertility in male patients are many, the shortened life expectancy of the parent being the obvious one. The ability to identify heterozygote carriers is another. Previously it was difficult, even with extensive family mapping, to identify heterozygote carriers, but the development of DNA probes which are able to recognise carriers with increasing certainty will alter this situation. Increasing the heterozygote carrier pool does not seem to be an important problem when considering the larger number already present in the community. The cost of treating infertility in male patients with cystic fibrosis, should it prove possible, would be considerable.

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The Authors

N D. Heaton, FRCS, formerly Urology Registrar. Now Senior Registrar in General Surgery, King's College Hospital.

J. P. Pryor, MS, FRCS, Consultant Urologist.

Requests for reprints to: N. D. Heaton, Firm III Office, King's College Hospital, Denmark Hill, London SE5 9RS.

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The Effect of Post-pubertal Varicocele on Testicular Volume

I. ERKAN, H. A. OZEN, A. ERGEN and F. REMZI

Department of Urology, Hacettepe University Medical Faculty, Ankara, Turkey

Summary—Paediatric varicocele is a well known entity but its effect on adult infertility has not been adequately clarified. Since measurement of testicular volume is currently the best method of estimating the male reproductive potential, 945 boys aged between 13 and 18 years were examined with regard to testicular volume and the incidence of varicocele.

The average volumes for right and left testes were 15.087 ± 0.237 and 14.514 ± 0.347 ml respectively, and the incidence of varicocele was 16.7%. The incidence increased from 14.5 to 21.7% as the ages increased from 14 to 18.

The differences in volume of the 2 testes in boys with varicocele were statistically significant when compared with the normal group, but this significance failed to become more pronounced when the slight varicocele group (grade I) was included with the normal group and compared with the severe varicocele group (grades II and III).

There may be no significant differences between the volumes of the 2 testes in boys with varicocele when careful measurement and strict statistical analyses are applied.

However, some boys in the varicocele group were found to have testicular volumes below the confidence interval (mean − SE) or under 1 SD, and the 2 testicular volumes differed in certain age groups. This group requires further follow-up.

The results of this study have added further contradictory findings to the issue of paediatric varicocele in terms of testicular atrophy, estimation of potential fertility and the indications for immediate surgery. There is a need for further prospective controlled trials.

The effect of paediatric varicocele on adult infertility has not yet been clarified. If surgical treatment is indicated, should it be applied to all children or only to those in whom infertility is anticipated?

It is generally agreed that testicular volume correlates well with semen quality and fertility, since the seminiferous tubules and germinal cells account for approximately 98% of the testicular mass (Sherins and Howards, 1986).

The purpose of this study was to determine testicular size in Turkish high school children, the incidence of post-pubertal varicocele and the effect of varicocele on testicular size.

Materials and Methods

The study was carried out on boys at a high school in Ankara. From a total of 1009 boys, 64 aged under 13 and above 18 years of age were excluded; thus the unselected study group comprised 945 boys. All were investigated by one consultant (I.E.) and varicoceles were graded according to the Dubin and Amelar classification (Lyon *et al.*, 1982).

Testicular size was assessed by measuring length and width with a caliper. All measurements were made by the same investigator (F.R.) after proper positioning of the boys.

The volume of the testes was assessed by using a modified empirical formula, *i.e.* testicular volume (in ml) $= (0.71 \times \text{length} \times \text{breadth})^2$, as described by Rundle and Sylvester (1962).

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The data for each parameter were analysed for differences among groups using analysis of variance, followed by Fisher's test for least significant difference using a computer and statistical software package.

Results

The average volumes for right and left testes of 945 boys were 15.087±0.237 and 14.514±0.347 ml respectively. The average testicular volumes according to age are shown in Table 1 and the Figure.

Of 945 boys aged between 13 and 18 years, 158 (16.7%) were found to have varicoceles. Grades I, II and III were diagnosed in 64, 58 and 36 boys respectively. The distribution of varicoceles according to age and grade is shown in Table 2. The incidence increased from 14.5% at the age of 14 to 21.7% at the age of 18. The condition was left-sided in all cases.

Table 1 Age Distribution and Average Testicular Volumes

Age (years)	*No. investigated*	*Right testis vol ±SE (ml)*	*Left testis vol. ±SE (ml)*
13	16	8.040±0.862	7.023±0.997
14	166	11.447±0.443	10.528±0.423
15	195	13.504±0.451	12.897±0.448
16	242	15.800±0.439	14.888±0.418
17	220	17.021±0.515	15.746±0.459
18	106	19.075±0.759	21.451±2.399
Total/ average	945	15.087±0.237	14.514±0.347

Statistical analysis of each line. $P>0.05$.

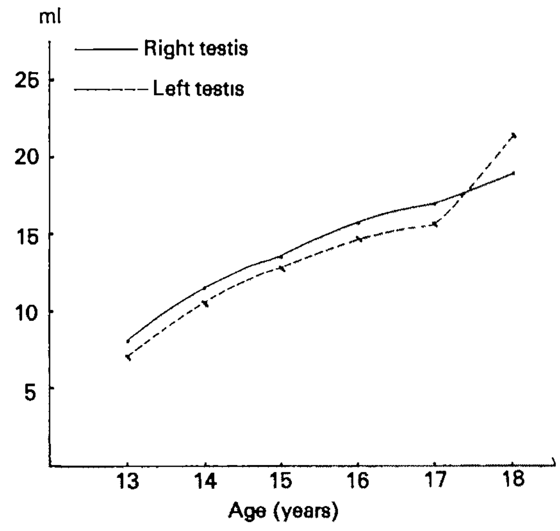

Fig. Average testicular volume with age

Table 2 Incidence of Varicocele

Age (years)	*No investigated*	*Grade*			*Incidence (%)*
		I	*II*	*III*	
13	16	1	3	–	25.00
14	166	7	9	8	14.45
15	195	15	12	4	15.89
16	242	13	10	7	12.39
17	220	20	14	12	20.90
18	106	8	10	5	21.69
Total/ average	945	64	58	36	16.72

The average testicular volumes in 787 boys without varicocele were 15.026±0.253 and 14.641±0.400 ml for right and left testes respectively. When these figures were compared with those of 158 boys with different grades of varicocele the volume difference between the 2 testes was found to be significant in the varicocele group (Table 3).

The volume differences according to the grade of varicocele were also investigated and the grades, when considered individually, did not have a significant effect on differential testicular volumes, although the volume of the left testis in boys with varicocele was always less than that of the right testis. These differences seemed to be greater than the difference between right and left testicular volumes in normal boys (Table 4).

Table 3 Testicular Volumes in Boys with and without Varicocele

	No.	*Right testis vol. ±SE (ml)*		*Left testis vol ±SE (ml)*	
Normal	787	15.026±0.253	(1)	14.641±0.400	(2)
Varicocele	158	16.015±0.383	(3)	14.329±0.570	(4)

Statistical analysis: $\left.\begin{array}{l}1:2\\1:3\\1:4\end{array}\right\}P>0.05$ $\quad 3:4\ P<0.05$

Table 4 Testicular Volumes and Grades of Varicocele

	No	*Right testis vol. ±SE (ml)*		*Left testis vol ±SE (ml)*	
Normal	787	(1)	15.026±0.253	(2)	14.641±0.400
Grade I	64	(3)	16.247±0.973	(4)	14.891±0.868
Grade II	58	(5)	16.064±1.046	(6)	14.323±0.985
Grade III	36	(7)	15.566±1.268	(8)	13.427±1.153

Statistical analysis. $\left.\begin{array}{ll}1:2 & 5:6\\3:4 & 7:8\end{array}\right\}P>0.05$

Since grade I varicocele is most prone to faulty diagnosis, differences in testicular volume were again compared after this group had been included with the normal group. Table 5 shows that the difference in volume between the 2 testes of boys with severe varicocele was greater than the difference in the normal plus grade I varicocele group, but this was not statistically significant.

Table 5 Differences in Testicular Volume between Normal + Grade I Varicocele Group and Severe Varicocele Group

	No.	*Right testis vol. ± SE (ml)*	*Left testis vol. ± SE (ml)*
Normal + Grade I	851	(1) 15.367 ± 0.243	(2) 14.929 ± 0.360
Grades II and III	94	(3) 15.863 ± 0.807	(4) 13.960 ± 0.751

Statistical analysis. 1:2 2:3 ⎫
1:3 2:4 ⎬ $P > 0.05$
1:4 3:4 ⎭

Table 6 Average Differences in Testicular Volume between Boys with and without Varicocele according to Age

Age (years)		*No*	*Right testis vol ± SE (ml)*	*Left testis vol. ± SE (ml)*
13	Normal	12	8.130 ± 0.959	7.562 ± 1.235
	Varicocele	4	7.771 ± 1.891	5.406 ± 1.146
14	Normal	142	11.643 ± 0.475	10.623 ± 0.438
	Varicocele	24	10.500 ± 1.204	9.966 ± 1.358
15	Normal	164	13.262 ± 0.483	12.890 ± 0.478
	Varicocele	31	14.783 ± 1.210	12.935 ± 1.241
16	Normal	212	15.767 ± 0.462	14.915 ± 0.453
	Varicocele	30	16.031 ± 0.371	14.694 ± 1.052
17	Normal	174	16.973 ± 0.552	16.030 ± 0.519
	Varicocele	46	17.201 ± 1.309	14.671 ± 0.967
18	Normal	83	19.324 ± 0.854	22.389 ± 3.018
	Varicocele	23	18.175 ± 1.641	18.065 ± 1.783

Statistical analysis of each line: $P > 0.05$

The volume differences between right and left testes when varicocele was present and absent were analysed according to age but the results were not statistically significant (Table 6).

The data were then screened to see how many of the varicocele group were below the confidence interval (mean − SE) or under 1 SD (standard deviation). There were 81 and 23 such cases respectively. Statistically significant differences between the 2 testicular volumes were noted in some age groups (Table 7).

Discussion

Comprehensive epidemiological studies of varicocele in the paediatric age group have shown that the incidence in boys aged between 10 and 19 years was 9 to 25.8% (Oster, 1971; Steeno *et al.*, 1976; Berger, 1980; Pozza *et al.*, 1983). The incidence of varicocele in the 945 boys in the present study was 16.7%. Horner (1960) stated that the greatest incidence (20.5%) was reached at the age of 14.5 to 15 years. This finding was confirmed by Oster (1971), but a statistically significant level could not be reached. Neither author could explain why varicoceles should disappear or decrease with time. In our study the incidence increased steadily with age and reached a plateau at the age of 18. We suggest that the development of varicocele in paediatric patients depends on multiple factors and "the increased blood flow during puberty" is not the only aetiological factor.

Since ethical considerations make it impossible to collect sperm or perform biopsies in this

Table 7 Average Differences in Testicular Volume between Boys with Varicocele and Extremely Low Testicular Volume

Age (years)	*No.*		*Right testis vol ± SE*		*Left testis vol ± SE*	
	SE(−)	*SD(−)*	*SE(−)*	*SD(−)*	*SE(−)*	*SD(−)*
13	1	1	4.181	4.181	2.178	2.178
14	13	4	6.142 ± 0.663	4.550 ± 0.647	4.781 ± 0.531	2.363 ± 0.261
15	17	3	9.924 ± 0.817	4.511 ± 0.671	7.649 ± 0.635	2.400 ± 0.110
16	15	3	11.493 ± 0.882	11.325 ± 3.249	9.926 ± 0.591	6.362 ± 1.115
17	24	7	12.746 ± 0.882	9.660 ± 1.673	10.115 ± 0.557	6.362 ± 0.437
18	11	5	11.837 ± 0.575	11.037 ± 0.378	10.869 ± 0.669	8.812 ± 0.236
Total	81	23				

Statistical analysis. For SE (−) Age lines 15 and 17 $P < 0.05$
For SD (−) Age lines 14, 15 and 18 $P < 0.05$.

particular age group, determination of testicular volume is usually the only important criterion for estimating male reproductive potential. There are 2 traditional methods for indirect measurement of testicular size. One involves measuring the longitudinal, transverse and the third axis of the testis with calipers and determining volume by an empirical formula: volume (in ml) = 0.71 × length × width × depth (Takihara *et al.*, 1983). Rundle and Sylvester (1962) simplified this formula on a practical level to: volume = $(0.71 \times \text{length} \times \text{breadth})^2$. The other method of estimating testicular volume is comparative palpation of the testes with testicular models of known volume. Both techniques have advantages, but there are considerable variations in the results according to each investigator and his method. Orchiometer estimations seemed to be more accurate than caliper measurements, since the correlation coefficients with the true testicular mass were found to be 0.58 and 0.81 with caliper and orchiometer respectively (Takihara *et al.*, 1983, 1987). Ultrasonography may also be used for testicular measurement, but although very accurate it is neither cost effective nor practical. We have used caliper measurements and tried to minimise errors by employing only 1 investigator for all measurements. Proper positioning of the boys avoided subcutaneous tissue, which is probably the main reason for overestimating testicular size. At least half of the patients with varicocele at puberty have atrophy of the affected testes (Steeno *et al.*, 1976; Okuyama *et al.*, 1988). Steeno *et al.* (1976) also found that the incidence of atrophy increased with the severity of varicocele. The definition of atrophy is subject to variation, however. Some workers recorded the comparative size of the testes on a relative basis, purely by gross palpation (Lyon *et al.*, 1982); some considered atrophy to be present only if a difference of 8% or 0.5 ml was detected between the 2 testes (Reitelman *et al.*, 1987) and others if a difference of 2 standard deviations was present between the affected testis and the testis in a normal age-matched population (Okuyama *et al.*, 1988).

Strict statistical analysis in the present study showed that the volume differences between right and left testes were significant in the varicocele group compared with the normal group when all varicocele cases were considered together. Although this significance was expected to be more pronounced when grade I cases were excluded, in fact it disappeared when this was done. This was a unique finding, since grade I varicoceles can be detected only by meticulous examination and thus are more prone to misdiagnosis, Steeno *et al.* (1976) showed that ipsilateral volume and consistency changes were not found in any child with small, grade I varicocele. Furthermore, if changes in testicular volume were analysed individually with each grade of varicocele, no significant differences were found.

On the other hand, there is a group of boys with varicoceles who have left testicular volumes below confidence intervals or under 1 SD of volumes in whom the differences between right and left testicular volumes are significant for certain age groups. These children should be followed up closely.

Apart from the sub-group mentioned above, failure to detect significant differences in volume between the 2 testes in boys with varicocele may be due to the method used to measure testicular size. The minute changes in testicular size that could be missed may obviate the expression of statistical significance.

It remains debatable whether a significant difference exists between the testicular volumes of boys with varicocele.

These observations have led us to conclude that borderline statistical significance in testicular volume differences can be ignored. This study has not solved the issue of varicocele, testicular atrophy and the question of immediate surgical treatment and has probably increased the number of contradictory findings. Prospective controlled trials over periods of 10 to 15 years are needed to provide a definitive answer regarding the treatment of paediatric varicocele.

Although this has been essentially a negative study in terms of the effect of varicocele on testicular volume, we shall study the boys with varicocele for at least 2 more years. Permission to do so has been given by the Ministry of Education and we are collaborating with the school staff.

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The Authors

I. Erkan, MD, Professor of Urology.
H. A. Özen, MD, Associate Professor of Urology.
A Ergen, MD, Associate Professor of Urology
F Remzi, MD

Requests for reprints to: I Erkan, Department of Urology, Hacettepe University Medical Faculty, Ankara, 06100 Turkey

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Case Reports

Acute Urinary Retention: A Unique Complication of Primary Varicella Infection of Childhood

R. M. NICHOLAS, S. SHARPE, W. J. H. GRAHAM and J. L. TEMPLETON, *Department of Surgery, Craigavon Area Hospital, Portadown, Northern Ireland*

Case Report

An 8-year-old boy presented with acute urinary retention 1 week after the onset of a classical primary varicella (chickenpox) rash. Examination confirmed a bladder palpable at the umbilicus. The prepuce was oedematous with a large vesicle on the glans penis obscuring the urethral meatus (Fig. 1).

Under general anaesthesia the vesicle was incised and drained. Passage of a urethral catheter was precluded by meatal induration; a 16F suprapubic catheter was therefore inserted (Fig. 2). Following removal of the suprapubic catheter the urethral urinary stream was unsatisfactory but was restored following dilatation of a meatal stricture. A rising antibody titre confirmed varicella-zoster infection.

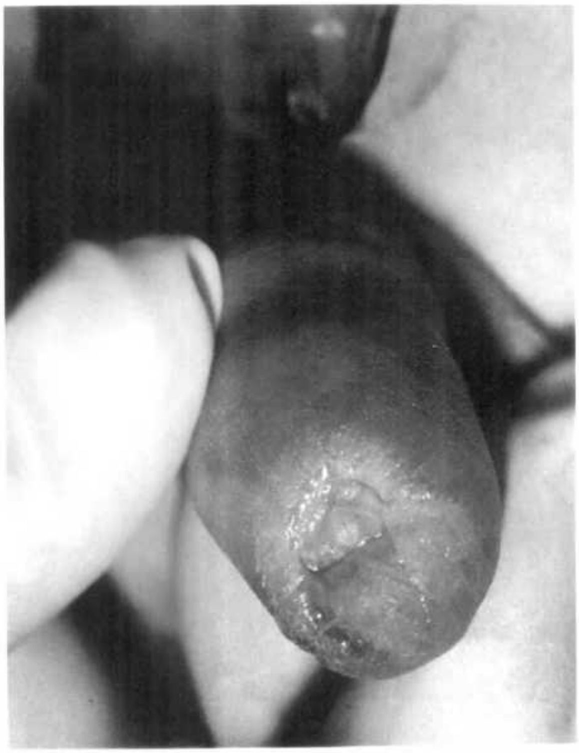

Fig. 1 Vesicle on glans penis with local oedema and induration.

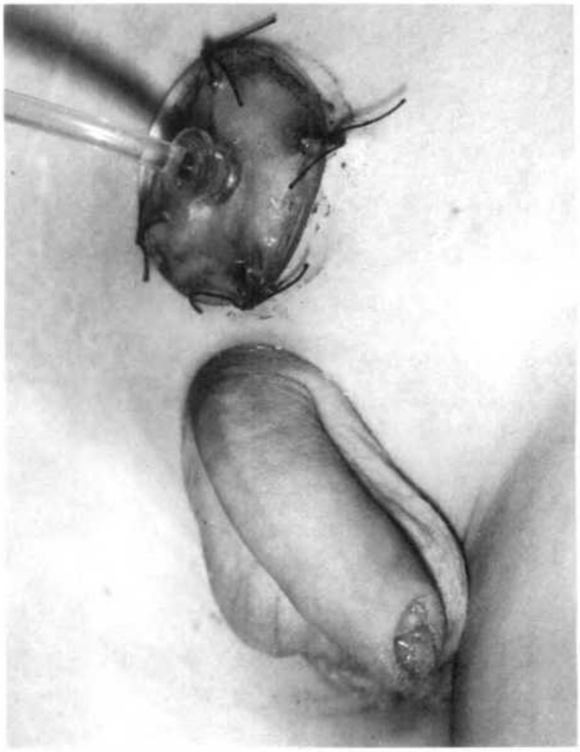

Fig. 2 Suprapubic catheter *in situ*. Chickenpox vesicle can be seen on the abdominal wall.

Comment

Primary exposure to the varicella-zoster virus usually produces systemic disturbance accompanied by widespread crops of vesicles (chickenpox). Herpes zoster (shingles) represents a reactivation of the virus in the dorsal root ganglion, producing the typical vesicular eruption in the corresponding sensory dermatome. Involvement of the sacral plexus resulting in urinary retention is well documented in shingles (Davidsohn, 1890; Rankin and Sutton, 1969; Richmond, 1974). However, we report acute urinary retention as a complication of chickenpox, an association which has not been reported previously.

The precise cause of the acute urinary retention in our patient is unclear. However, it is possible that the following factors were involved: the neurogenic effect of primary varicella infection on the sacral plexus; the mechanical effect of the vesicle and associated induration occluding the external urethral meatus; the discomfort experienced when attempting micturition.

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Requests for reprints to: R. M. Nicholas, Department of Orthopaedic Surgery, Queen's University of Belfast, Musgrave Park Hospital, Belfast BT9 7JB.

Hydrops tubae profluens—not a Genitourinary Fistula but a Diagnosis to be Missed

E. P. PERRY and J. G. SMART, *Department of Urology, Leicester General Hospital, Leicester*

Case Report

A 50-year-old lady presented with acute left iliac fossa pain and a 3-month history of vaginal discharge, initially brown and later clear. Ultrasound showed a cystic right ovary and deviation of the uterus to the left. An intravenous urogram demonstrated a large central filling defect of the bladder (Fig. 1). Urological opinion was sought and cystoscopy disclosed no intravesical lesion, there being a bi-manually palpable cystic lesion between the bladder and the uterus. A gynaecologist performed a dilatation and curettage; clear fluid issued from the cervix and curettings were normal. A hysterosalpingogram showed that the left fallopian tube was abnormally sited and contrast was seen in what was considered to be the bladder (Fig. 2); the patient was again referred to the urologist as having a probable genitourinary fistula. The fluid was not urine, having an osmolality of 309 and urea of 4.4 mmol/l. At urological laparotomy, bilateral hydrosalpinges were found and panhysterectomy was performed. Convalescence was normal. Histological examination reported bilateral primary papillary carcinoma of the fallopian tubes.

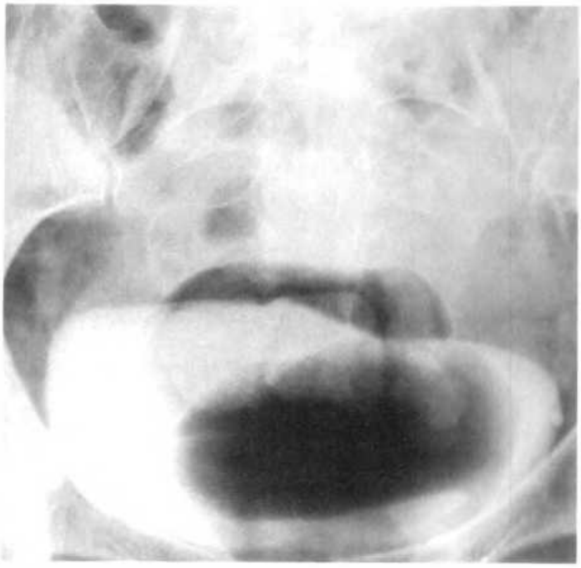
Fig. 1

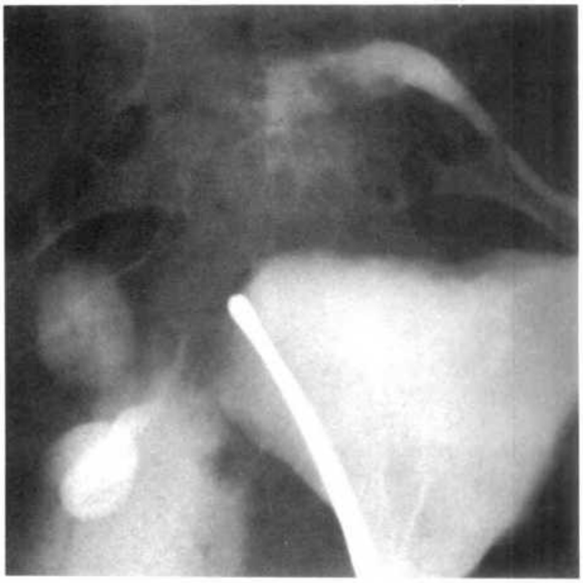
Fig. 2

Comment

Primary carcinoma of the fallopian tube is rare, with an incidence of 0.3 to 1.1% of female genital carcinomata; 25% are bilateral (Sedlis, 1961). The diagnosis is rarely made pre-operatively (Eddy *et al.*, 1984), but intermittent vaginal discharge with a diminishing adnexal mass (hydrops tubae profluens) is suggestive of fallopian tube malignancy (Sinha, 1959).

It is suggested that urologists dealing with numbers of genitourinary fistulae should keep this condition in mind, since their gynaecological colleagues may have been misled towards the diagnosis of a fistula.

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Requests for reprints to: E. P. Perry, Department of Surgery, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX.

Actinomycosis Causing Ureteric Obstruction

R. J. BUTTERWORTH, D. G. L. DAVIES and A. J. L. HART,
Departments of Surgery and Urology, East Glamorgan General Hospital, Pontypridd

Case Report

A 42-year-old housewife presented with a 6-month history of intermittent lower abdominal pain, with no associated symptoms.

Six years previously she had had an appendicectomy, histology of which showed peritonitis from without. She had used an IUCD (SAF-T-COIL) for 15 years.

Examination showed mild left iliac fossa tenderness only. FBC, urea, electrolytes and serum creatinine were normal. Erythrocyte sedimentation rate was raised (110 mm/h). An intravenous urogram showed an obstructed right kidney (Fig. 1) with a stricture in the lower third of the ureter.

Cystoscopy was normal and a stent was inserted into the ureter, causing a radiological improvement in function.

An open exploration of the ureter was undertaken. An extensive infiltrating mass, containing pockets of cheesy material, filled the lower abdomen and pelvis. Frozen section suggested an inflammatory process and resection was not attempted.

Histology of biopsies showed microabscesses containing *Actinomyces* (Fig. 2).

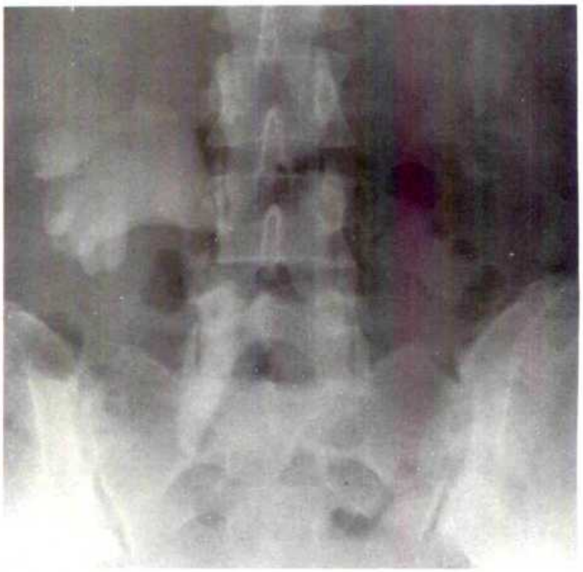

Fig. 1

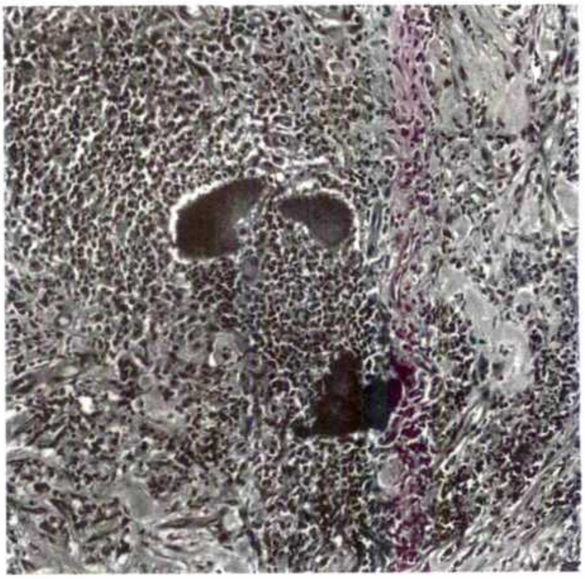

Fig. 2

A 12-week course of ampicillin was given and the IUCD removed.

Six months later the stent was removed and subsequent intravenous urography was normal. The patient remains asymptomatic.

Comment

Ureteric obstruction due to actinomycosis has rarely been described (Fulton *et al.*, 1981; Brown and

Bancewicz, 1982). Most cases have been associated with the use of an IUCD. Surgical intervention, except for the purposes of diagnosis, seems unnecessary; all patients whose progress has been reported have resolved on antibiotic therapy alone.

It is important to consider this diagnosis in patients with ureteric obstruction, since organisms may be sparse in tissue section and cultures negative (Davies and Keddie, 1973).

Acknowledgements

We are grateful to Dr D. Stock, Department of Pathology, East Glamorgan Hospital, for his advice, and to Mrs W. Gore for secretarial assistance.

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Requests for reprints to: A. J. L. Hart, Department of Urology, East Glamorgan General Hospital, Church Village, Nr. Pontypridd, Mid Glamorgan CF38 1AB.

The AS 800 Urinary Sphincter in Renal Transplantation

A. GELET, R. SANSEVERINO, M. SALAS, X. MARTIN, J. M. MARECHAL and J. M. DUBERNARD, *Department of Urology and Transplantation, Hôpital Edouard Herriot, Lyon, France*

Case Report

A 15-year-old white male with spina bifida presented in 1982 with chronic renal failure due to a neurogenic bladder, with bilateral hydronephrosis and pyelonephritis. Urodynamic investigations showed a neurogenic bladder with external sphincter stenosis. Following endoscopic sphincterotomy in 1982 the patient became completely incontinent during the day and partly incontinent at night. His renal function deteriorated progressively. Serum creatinine rose to 600 μmol/l by the end of 1984 and severe hypertension developed. The patient started haemodialysis in 1985. Urodynamic investigations confirmed high intravesical pressure with incontinence when bladder filling exceeded 250 ml, but anticholinergic drugs drastically reduced the intravesical pressure. The patient was considered suitable for a cadaver kidney transplantation followed by implantation of an artificial sphincter 1 or 2 months later.

In February 1987 the patient received a cadaver kidney. Immunosuppressive therapy consisted of azathioprine, prednisone and monoclonal antibodies. Cyclosporin A was introduced on the 19th post-operative day and monoclonal antibodies were discontinued on day 21. The early post-operative period was marked by a sharp decrease in serum creatinine to 140 μmol/l by day 25.

The patient was discharged 1 month after transplantation with good renal function and complete urinary incontinence. Full-dose anticholinergic drugs were given in view of the need to implant an artificial urinary sphincter.

This operation was performed 4 months after transplantation. A pre-operative urinary infection was treated with an aminoglycoside and a β-lactamine. A voiding cystourethrogram showed no reflux into the transplant and complete bladder voiding. The sphincter was placed via a suprapubic mid-line incision; freeing the bladder neck was difficult, requiring a large cystotomy to verify the position of the cuff. A 9-cm cuff was placed around the bladder neck, the reservoir was placed in the left prevesical space (contralaterally to the kidney transplant) and the pump was placed in the right scrotum (Fig. 1). The system was deactivated, an indwelling urethral catheter was left in place, and the prevesical space was drained for 24 h.

In the early post-operative period the patient experienced an increase in serum creatinine to 334 μmol/l; aminoglycosides were considered responsible and were

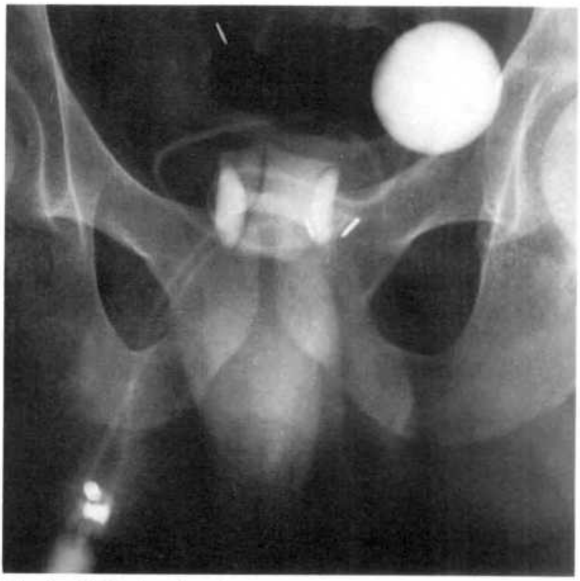

Fig. 1 KUB showing placement of the various elements of the artificial urinary sphincter.

stopped. Urinary cytology confirmed tubular toxicity and ultrasound excluded any mechanical cause. A steroid pulse (4 mg/kg/day) was given 2 days later because renal function failed to improve despite having stopped antibiotics.

The urethral catheter was removed on the 12th postoperative day and the patient was discharged on day 30 with the sphincter deactivated and a serum creatinine of 180 μmol/l.

One month later (2 months after sphincter placement), urethral fibroscopy showed good position of the cuff and no urethral erosion. A second cystourethrogram confirmed the absence of reflux and perfect bladder voiding. The sphincter was activated and continence immediately obtained. Anticholinergic drugs were stopped and the patient left hospital 48 h later perfectly continent; we asked him to empty his bladder every 3 h to avoid retrograde pressure on the kidney graft.

In November 1987 the patient presented with a serum creatinine of 350 μmol/l and a proteinuria of 7 g/24 h. Renal biopsy confirmed rejection and he was treated with a steroid pulse (4 mg/kg/day) and with ALG for 10 days. The proteinuria disappeared and creatinine decreased to 180 μmol/l.

At the last out-patient visit, in November 1988, the patient was continent; he had a serum creatinine of 210 μmol/l, no urinary infections and a proteinuria of 0.9 g/24 h, without nephrotic syndrome. The cystourethrogram showed good bladder compliance (500 ml), with no reflux into the graft, normal voiding with a good urinary stream (Fig. 2A) and no residual urine after voiding (Fig. 2B).

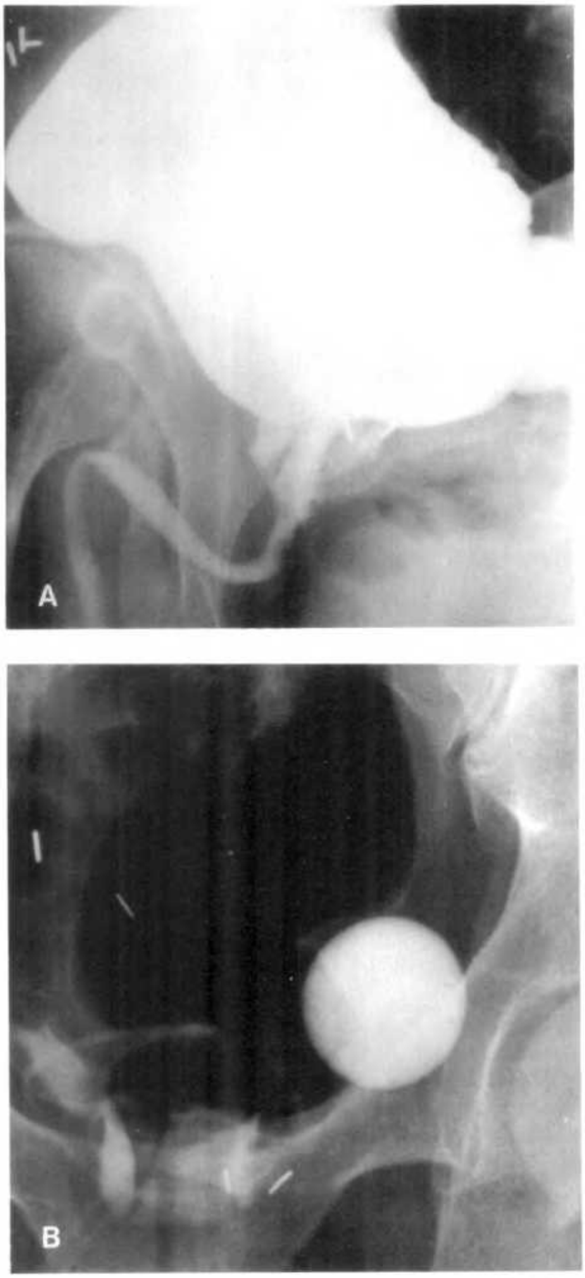

Fig. 2 Voiding cystourethrogram showing (A) good bladder neck opening and urinary stream and (B) no residual urine after micturition.

Comment

Recent improvements in artificial urinary sphincter devices have contributed to their widespread use (Goldwasser *et al.*, 1987). The use of an AS 800 urinary sphincter in renal transplantation has been described by Thomalla *et al.* (1988). We now report the second case in the literature. Thomalla *et al.* (1988) emphasised the risk of infective complications and considered that pre-transplant placement of the sphincter reduced this risk.

We believe that an alloplastic device should be inserted a few months after transplantation, when renal function is usually stable, the immunosuppressive regimen has been reduced and the risk of infection is less (Sidi *et al.*, 1987).

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Requests for reprints to: R. Sanseverino, Department of Urology, Hôpital E. Herriot, Place d'Arsonval, 69437 Lyon, France.

Urethralisation of the Female Phallus with Absent Urogenital Sinus

P. K. H. TAM, D. H. PARIKH and A. M. K. RICKWOOD,
Department of Urology, Royal Liverpool Children's Hospital (Alder Hey), Liverpool

Case Report

The patient was the product of an uneventful pregnancy, with no history of maternal virilisation or androgen ingestion. At birth she was noted to have imperforate anus, hypoplastic labia majora, with no vulval orifice, and a markedly enlarged clitoris with well developed corpora and a glandular urethral orifice (Fig. 1). The abdomen was grossly distended by a mass arising from the pelvis, containing both gas and fluid and which, at laparotomy, proved to be an enormously distended vagina into which gas had passed via a recto-vaginal fistula and urine via a urethral fistula (Fig. 2). The uterus, fallopian tubes and ovaries were normal. After vaginal decompression, the recto-vaginal fistula was divided and oversewn and the bowel brought out as a terminal colostomy. Postoperatively, although voiding occurred via the clitoral meatus, urine reaccumulated within the vagina and required the formation of a cutaneous vesicostomy. Subsequent investigations showed an XX karyotype, with normal steroid metabolism, crossed fused renal ectopia, right vesicoureteric reflux and subluxation of the left hip. A degree of hydroureteronephrosis seen on neonatal ultrasound examination resolved following the vaginal decompression. The phallic urethra, although somewhat narrow, accommodated an 8 F endoscope.

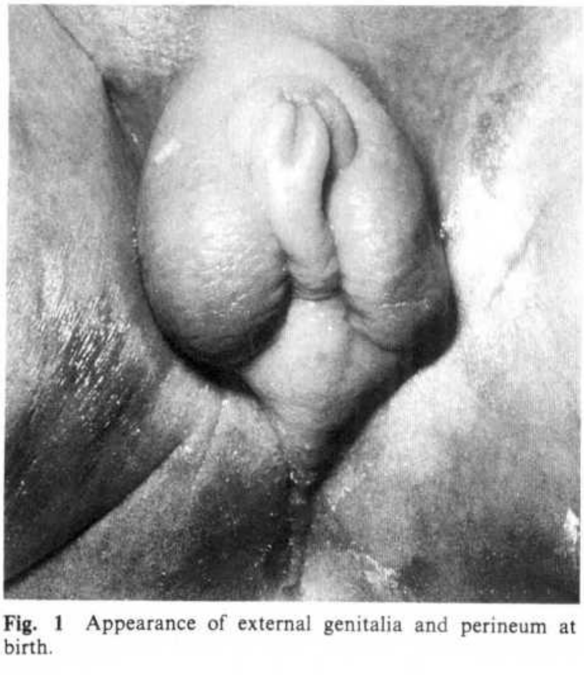

Fig. 1 Appearance of external genitalia and perineum at birth.

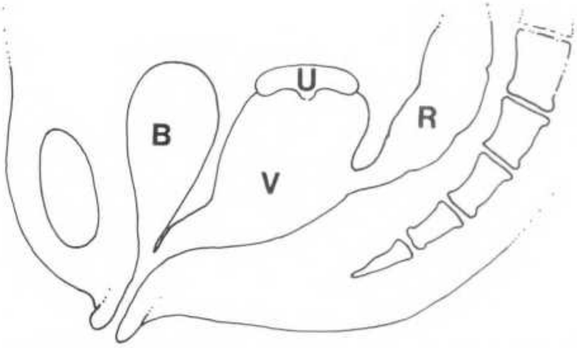

Fig. 2 Diagrammatic view of pelvic anatomy showing relationships of bladder (B), vagina (V), uterus (U) and rectum (R).

At 10 months of age, a posterior sagittal approach (Pena and deVries, 1982) provided excellent exposure of the vagino-urethral fistula, which was divided and oversewn. The colostomy was taken down and rectum and vagina were brought to their normal perineal positions. A covering transverse colostomy was closed 2 months post-operatively and the vesicostomy 2 months later. Clitoral reduction with vulval repositioning of the urethral meatus is intended.

Comment

This case cannot be accommodated within recognised patterns of female pseudohermaphroditism or of anorectal anomalies. The clitoral hypertrophy bears some resemblance to the virilising syndromes, notably adrenocortical hyperplasia, although a glandular meatus in the presence of relatively modest clitoral enlargement would be unusual with such conditions. Moreover, there was no evidence of any virilising factor in the case, whilst the concomitant rectal and upper urinary tract anomalies form no part of these syndromes. Similarly, clitoral enlargement with a phallic urethra and atresia of the distal vagina are not features of imperforate anus with recto-vaginal fistula.

The clitoral and vulval deformities were reminiscent of a case of urethralisation of the female phallus previously described by Turnock and Rickwood (1987). As with the present case, an appreciable proportion of girls with this rare condition also have a recto-vaginal fistula and primary anomalies of the upper renal tracts (Bellinger and Duckett, 1982). However, a feature common to all recorded examples of urethralisation of the female phallus, but absent in this instance, is duplication of the urethra immediately below the bladder neck with a relatively fine accessory phallic urethra and a principal urethral channel passing posteriorly to enter a common urogenital sinus. Despite the absence of this feature in the present case, we believe it is best regarded as a unique variation upon the theme of urethralisation of the female phallus. Since the embryogenesis of this anomaly is unknown it is pointless to speculate as to what further aberrations may have occurred in this instance.

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Requests for reprints to: P. K. H. Tam, Department of Paediatric Surgery, Institute of Child Health, Royal Liverpool Children's Hospital (Alder Hey), Eaton Road, Liverpool L12 2AP.

Iatrogenic Torsion of an Undescended Testis

N. BEECHEY-NEWMAN and D. HARRISS, *Department of Surgery, Wycombe General Hospital, High Wycombe*

Case Report

An 8-month-old boy who had been an in-patient with gastroenteritis for 2 days was found to have an undescended left testis. Despite repeated careful examination the left testis was not palpable either in the scrotum, superficial inguinal pouch or in the inguinal canal. The right testis was normally descended. Before discharge, therefore, an appointment was made for the child to attend the surgical out-patient department.

The child had been home little more than 3 h when he became fretful and his mother noted a tender swelling in the left groin. He returned to hospital, where a large tender swelling was obvious at about the level of the deep inguinal ring. The mass did not have a cough impulse and even after sedation and elevation would not reduce at all.

He underwent urgent surgical exploration and a hernial sac containing an ischaemic but morphologically normal testis was found. The spermatic cord was twisted through 2 complete revolutions but on rectifying this a pink colour returned. Bilateral orchiopexy was performed and the left inguinal hernia repaired.

Comment

The mechanism of torsion of a scrotal testis is said to involve abnormal forces created by the cremaster muscle in the presence of the "bell-clapper" deformity (Phillips and Holmes, 1972). In the ectopic position, angulation of the cord may predispose to torsion after abdominal wall contractions such as fitting (Johnson and Holmes, 1964). Canalicular torsion is, however, rare. We propose a possible iatrogenic cause, namely that of repeated clinical examinations while in hospital. Frequent vomiting could have been an additional predisposing factor.

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Requests for reprints to: N. Beechey-Newman, Department of Surgery, Wycombe General Hospital, High Wycombe HP11 1TT.

Primary Osteosarcoma of Penis

A. T. EDWARDS and J. J. F. SOMERVILLE, *Departments of Pathology and Urology, Halifax General Hospital, Halifax*

Case Report

A 72-year-old man presented with a penile tumour. Examination showed a discoloured papillary mass 5 × 4 × 3 cm involving the lateral aspect of the glans penis (Fig. 1). Partial penectomy was performed and histological examination of the tumour showed the appearances of osteosarcoma characterised by malignant osteoid and chondroid proliferation superimposed upon a malignant spindle cell stroma (Fig. 2). Clinical examination, X-ray skeletal survey, isotope bone scan and CT scan of abdomen and pelvis showed no other tumour.

Four months later the patient developed a tumour mass

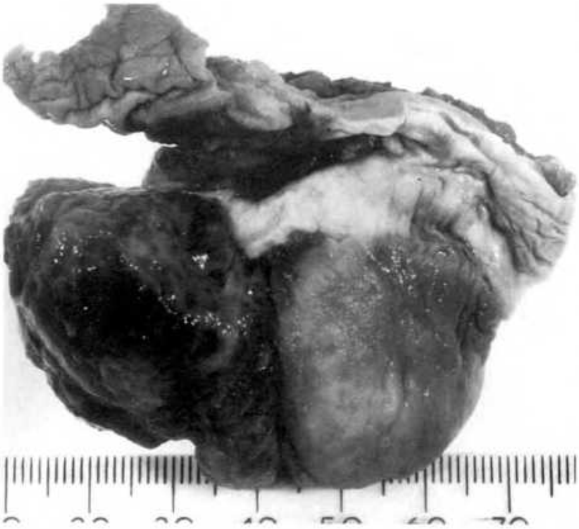

Fig. 1

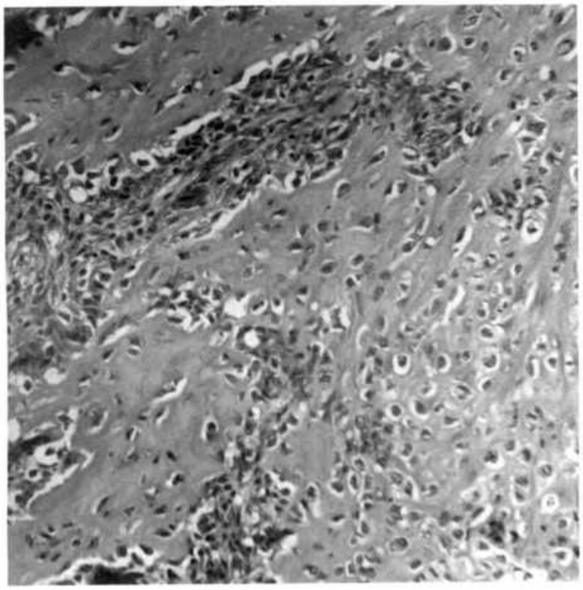

Fig. 2

6 cm in diameter in the left groin, which was removed. Histological examination showed appearances similar to those of the original penile growth. Following the second operation he was referred for radiotherapy, but his condition deteriorated rapidly and he died 6 months after the initial presentation. Autopsy was not performed.

Comment

Extra-osseous osteosarcoma is a rare tumour and 80% of cases occur in extremities and limb girdles (Sordillo *et al.*, 1983). Within solid organs the tumour is particularly uncommon, although cases have been recorded in the genitourinary system, notably kidney, bladder and uterus, with a solitary example in the testis.

Primary sarcomas of the penis are rare and although a variety of histological types have been described (Saw *et al.*, 1986), we have found only 1 reference to osteosarcoma (Shrikhande and Sirsat, 1969). In that particular instance the osteosarcoma occurred in conjunction with squamous carcinoma as part of a mixed mesenchymal and epithelial tumour.

Our case fulfils the criteria for the diagnosis of a primary extra-osseous osteosarcoma and we have been unable to find any other reference to a pure primary osteosarcoma of the penis in the medical literature. Such tumours tend to occur in older age groups compared with the primary osteosarcomas of bone. The prognosis, however, is equally poor, with a 5-year survival rate of less than 15% and 80% dead within 2 to 3 years.

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Requests for reprints to: A. T. Edwards, Department of Pathology, Royal Halifax Infirmary, Free School Lane, Halifax HX1 2YP.

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0007–1331/90/0066–0554/$10.00

Points of Technique

Suprapubic Catheterisation Using a Guidewire and Dilators

R. I. McMULLIN, *Department of Urology, Fremantle Hospital, Fremantle, Australia*

There remain many indications for a suprapubic catheter (SPC). Occasionally, an SPC is required for several weeks or longer. In these circumstances a large bore Foley catheter is preferable to catheters designed for percutaneous insertion, which tend to be of small calibre, flimsy and easily dislodged.

A technique for introducing a Foley catheter is described. It can be performed under local anaesthesia and requires no special equipment except for a guidewire and percutaneous tract dilators.

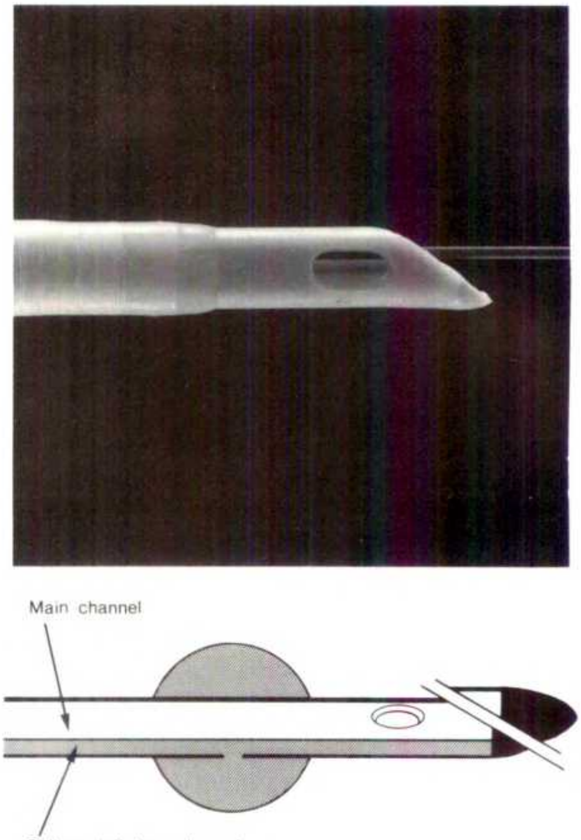
This method has been used on 6 occasions. Local anaesthesia was used on 4 occasions and general anaesthesia twice, in combination with cystoscopy and examination under anaesthesia.

Technique

After ensuring that the bladder is full, the midline suprapubic site is prepared and the skin and subcutaneous tissues are infiltrated with lignocaine. A 5 to 10 mm midline suprapubic incision is made. The linea alba is also incised to facilitate dilatation of the percutaneous tract.

A J-wire can be introduced into the bladder using a 16 G intravenous cannula or a standard percutaneous nephrolithotomy needle. Placement in the bladder is confirmed when urine flows from the cannula prior to insertion of the J-wire. The tract is dilated over the guidewire using standard percutaneous tract dilators (both Storz and Amplatz systems have been used). The tract is dilated beyond the diameter of the catheter to facilitate passage of the catheter over the guidewire (*i.e.* to 20 F for a 16 F catheter). With the guidewire in the bladder, the dilators are removed and the catheter passed over the guidewire.

The siliconised Foley catheter must be modified so that it can be passed over the guidewire. The tip of the catheter is cut obliquely in order to open into the central lumen without interfering with the balloon inflation channel (Figs 1 and 2). The balloon should be tested prior to passing the catheter over the guidewire into the bladder.



Figures 1 and 2 The tip of the catheter is cut obliquely, using a scalpel, so that it can be passed over the guidewire without intefering with the balloon inflation channel.

The procedure was successful and well tolerated in all 6 cases. There was no difficulty in passing the catheter over the guidewire and no case of balloon failure. All patients were discharged within 24 h or when they had learned to care for the catheter and bag. All catheters were removed or replaced 6 weeks later and there were no cases of encrustation at the cut end of the catheter.

Comment

Stab techniques for suprapubic catheterisation have a number of limitations and the immediate insertion of a sturdy SPC is often desirable. Equipment for dilating a percutaneous tract is readily available to most urologists. Such a method of introducing a urinary catheter under local anaesthesia is described. It has proved to be rapid, safe and reliable.

Requests for reprints to: R. I. McMullin, 198 South Terrace, Kensington 6151, Western Australia.

Introduction of a Foley Catheter by Puncture Suprapubic Cystostomy

B. ELEM, *Department of Surgery, University of Zambia, Lusaka, Zambia*

Failed catheterisation in the presence of an acutely distended bladder is not an uncommon clinical problem. The recent introduction of the Nottingham trocar and sheath (Lawrence *et al.*, 1989) is a notable advance towards achieving bladder decompression in such a situation by suprapubic insertion of a Foley catheter. The disposable nature of this device makes it ideally suitable for use in developed countries; recurring expenses, however, will make its routine employment in many third world hospitals highly impractical. The following is an account of a non-disposable suprapubic Foley catheter introducer which has been devised by the author and used without complications in the University Teaching Hospital, Lusaka, Zambia.

The Lusaka puncture suprapubic cystostomy set consists of a sharp pointed metal trocar and a malleable metal outer cannula split along its entire length (Fig. 1). The same cannula can be used by wrapping it around trocars of smaller sizes. The sheath, when maximally open, allows easy introduction of a 22 F Foley catheter. The components of the device can be effectively sterilised both by autoclaving and immersion in chemicals.

Technique

After local anaesthetic infiltration to the skin and deeper tissue, a transverse incision marginally wider than the diameter of the trocar is made 2 cm above the symphysis pubis strictly in the midline. Having confirmed the presence of a distended bladder by aspirating clear urine with a hypodermic needle, the trocar with the overlying sheath is inserted into the bladder by a firm downward rotating pressure. Entrance of the trocar into the bladder is always associated with the sensation of a sudden "give". The catheter is inserted immediately following removal of the trocar before the bladder drains completely. After inflation of the balloon the sheath is withdrawn from the bladder and removed simply by sliding it over the catheter (Fig. 2). To avoid complications the following precautions should be meticulously observed: (1) the procedure should not be undertaken in the absence of a distended bladder; (2) the trocar must be inserted

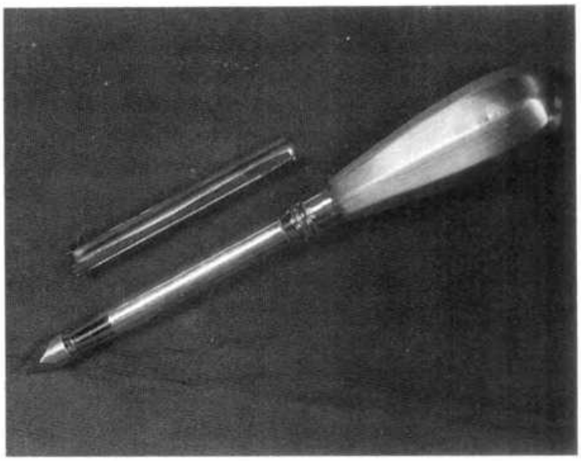


Fig. 1 The Lusaka trocar and cannula.

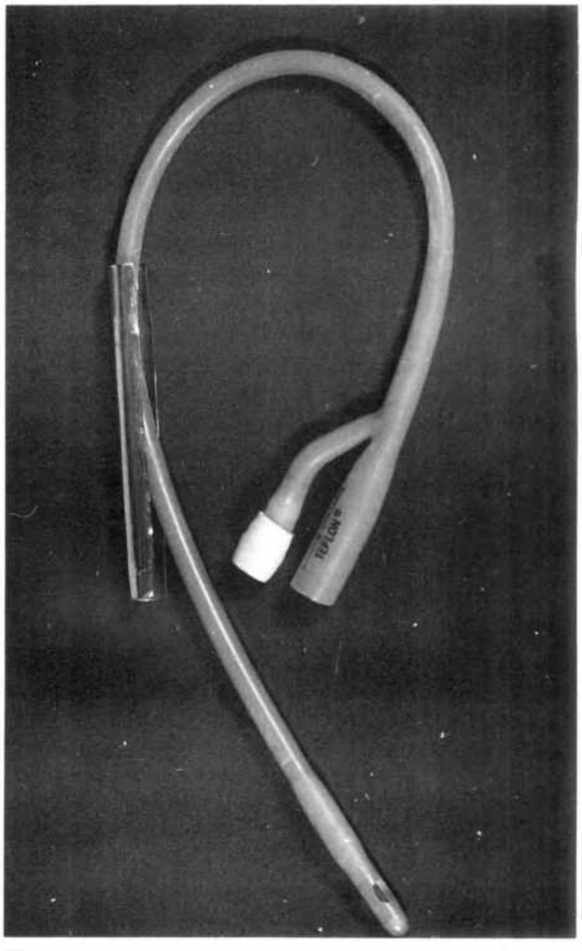


Fig. 2 After withdrawing from the bladder, the sheath is removed by simply sliding it over the catheter.

in a rigidly perpendicular fashion without any slant; (3) it is best avoided in the presence of a suprapubic surgical scar.

Acknowledgement

I thank the staff of the Medical Illustration Unit, University of Zambia, for help with the illustrations

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Requests for reprints to: B. Elem, Department of Surgery, University of Zambia School of Medicine, P O. Box 50110, Lusaka, Zambia.

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Correspondence

Dear Sir,

re **Relationship between intermittent hydronephrosis and megacalicosis.** P. H. O'Reilly. *Br. J. Urol.*, **64**, 125–129, 1989.

Neither of these 2 cases presented fulfils the urographic criteria that should be used to diagnose megacalices. The shape of the renal pelvis and its junction with the ureter are wrong in both cases. The pelvis must funnel *gradually* at its transition into the ureter. Abrupt narrowing at the pelviureteric junction should make one resist the diagnosis of megacalices. Nevertheless, I agree with the author that there are rare patients whose urographic images really do look like megacalices and yet prove to be obstructed. The 2 cases presented do not qualify, however.

I encourage the use of the term "megacalices" rather than "megacalicosis" for *bona fide* cases. Otherwise, won't we be stuck with primary megaureterosis, megacystosis and megaurethrosis?

Yours faithfully,

L. B. Talner
University of California, San Diego Medical Center, San Diego, California 92103, USA.

Reply from Mr O'Reilly. Dr Talner's comments are useful to clarify further the important distinction between megacalices and obstructive uropathy. The point is that the radiographic appearances presented strongly *resemble* megacalices, but are completely atypical of pelviureteric junction (PUJ) obstruction, showing a dependent PUJ, a mildly distended rather than dilated renal pelvis, and no objective radiographic evidence of obstruction. In case 1 in particular, there is no abrupt narrowing at the PUJ. Most urologists would be reluctant to label these cases as obstructive uropathy without further objective evidence to support such a diagnosis.

Dr Talner's uroradiological reputation is known to us all on both sides of the water. I welcome his comments but the message of the paper, not to assume megacalices without excluding obstruction first, stands. He will at least be pleased to note that I am more than happy to adopt the terminology he recommends.

Dear Sir,

re **Giant posterior urethral calculus.** A. Bolukbasi and B. Gumus. *Br. J. Urol.*, **65**, 301–302, 1990.

The authors present the case of an ellipsoid urethral calculus measuring 72 × 52 × 49 mm which they qualify as "a giant calculus" and mention that it appears to be the largest stone described in the literature.

A similar claim was made for what was called "a massive urethral stone" measuring 90 × 50 mm (*N.Y. State J. Med.*, **68**, 810–811, 1978).

In fact, the 3 largest urethral stones ever reported are:

(1) A stone measuring 95 × 40 × 30 mm and weighing 43 g which was removed from the urethra 4 years after suprapubic prostatectomy (F. S. Haddad (1958). *Proc. XI Congrès International d'Urologie*. p. 391).

(2) A stone measuring 96 × 65 × 50 mm and weighing 90 g which was removed 7 years after perineal prostatectomy (F. S. Haddad (1958). *Proc. XI Congrès International d'Urologie*. P. 391).

(3) A stone measuring 100 × 100 mm which was removed 28 months after radical retropubic prostatectomy (F. S. Haddad (1986). *J. Urol.*, **136**, 123–126; F. S. Haddad (1990). *Urol. Int.* (In press)).

Yours faithfully,

Farid S. Haddad
Chief of Urology, Carl T. Hayden Veterans Administration Medical Center, Phoenix, Arizona, USA.

Reply from Dr Bolukbasi. We thank Professor Haddad for his letter but wish to draw attention to the fact that the urethral calculus we described was confined to the bulbo-membranous urethra in a patient with a neurogenic bladder disorder. It had developed following the application of a penile clamp for incontinence. The patient had not undergone previous prostatectomy, nor did it extend into the bladder as a "mushroom" calculus as has been described by Dr Haddad. In both of these situations much larger stones have been observed, including a mushroom calculus in one of our own patients that measured 100 × 45 × 65 mm. As the aetiology, location and extent of the calculus in our patient differed from those described previously, we considered it to be of interest.

British Journal of Urology (1990), 66, 558

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Glasgow. 25–28 June 1991

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 4 January 1991.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

British Journal of Urology (1990), 66, 559–560

Diary

1991

January 4	Final date for submission of abstracts for 1991 BAUS Annual Meeting.
January 14–February 1	Short Courses in Urology and Nephrology including: Disorders of Bladder Function, Reconstructive Surgery, Disorders of the Female Urinary Tract, Urological Trauma and Emergencies, Acute and Chronic Renal Failure, Transplantation, Management of Stones and Upper Tract Obstruction, Endoscopic Urology and Recent Technological Advances in Urology, The Retroperitoneum, Surgical Techniques, Urological Problems in the Elderly. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
y 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
uary 3–6	International Conference on Orgasm. New Delhi, India. Contact Professor Prakash Kothari, First International Conference on Orgasm, 203 A, Sukhsagar. N. S. Patkar Marg, Bombay 400 007, India.
February 7–8	Uro-Radiology '91. For further details of this course please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
February 23–March 2	Royal Society of Medicine, Section of Urology, Vail, Colorado. Contact: M. H. Ashken, Consulting Rooms, BUPA Hospital, Old Watton Road, Colney, Norwich NR4 7SZ.
March 11–15	Uro-Andrology Course including Male Infertility and the Management of Impotence. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
March 16–17	International Symposium of Operative Andrology. For further details of this course and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
April 8–28	Short Courses in Urology and Nephrology including: The Management of Benign and Malignant Prostatic Disease, Paediatric Urology, The Management of Urological Cancers, Tropical Diseases and GU Medicine, Reconstructive Surgery. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
April 12–13	Second Meeting of European Society of Paediatric Urology, Beaune, France. "Neurogenic Bladder in Children and Adolescents". Contact: Dr P. Mouriquand, "Le Dizenier", 11 Impasse Mouillard, 69009 Lyon, France.
June 2–6	American Urological Association, Metro Toronto Convention Centre, Toronto, Canada.
June 7–8	Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindernburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09.

June 16–20	Canadian Urological Association Annual Meeting, Ottowa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
June 17–22	Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
June 18–22	Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands.
June 25–28	BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
July 2–3	Diploma Course Examination. For further details of these courses and meeti please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Ave London WC2H 8JE. Tel: 071 240 9115.
September 1–6	6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Ser Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungar Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.
September 16–19	Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.
1992	
January 10	Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
May 10–14	American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
June 21–26	BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
June 22–25	Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
August 24–27	Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
1993	
May 16–20	American Urological Association, San Antonio Convention Centre, San Antonio, Texas.
June 13–17	Canadian Urological Association Annual Meeting, Toronto. Contact: Dr R. B. Auld, Suite 620, 5991 Spring, Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
1994	
May 15–19	American Urological Association, Moscone Centre, San Francisco, California.

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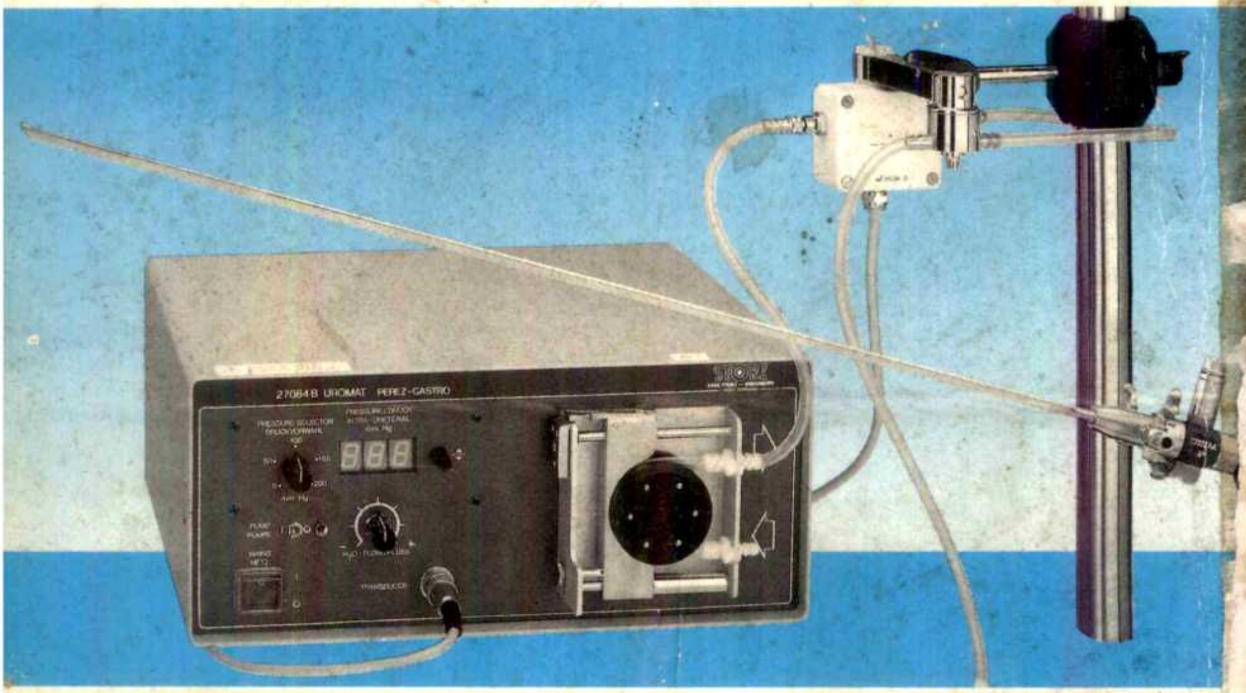

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Teletex: 746 118, Telefax: (0 74 61) 70 81 05

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